or prognose, inflammatory conditions, both chronic and acute conditions, including, but not limited to, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, and resulting from over production of cytokines (e.g., TNF or IL-1.).

Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

Additional preferred embodiments of the invention include, but are not limited to, the use of polypeptides, antibodies, polynucleotides and/or agonists or antagonists in the following applications:

Administration to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

Administration to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741.

A vaccine adjuvant that enhances immune responsiveness to specific antigen.

An adjuvant to enhance tumor-specific immune responses.

An adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, Respiratory syncytial virus, Dengue, Rotavirus, Japanese B encephalitis, Influenza A and B, Parainfluenza, Measles, Cytomegalovirus, Rabies, Junin, Chikungunya, Rift Valley fever, Herpes simplex, and yellow fever.

An adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae, Mycobacterium leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli,* Enterohemorrhagic *E. coli*, *Borrelia burgdorferi*, and Plasmodium (malaria).

An adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria).

As a stimulator of B cell responsiveness to pathogens.

As an activator of T cells.

As an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

As an agent to induce higher affinity antibodies.

As an agent to increase serum immunoglobulin concentrations.

As an agent to accelerate recovery of immunocompromised individuals.

As an agent to boost immunoresponsiveness among aged populations.

As an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

As an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

As an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, recovery from surgery.

As a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonization of

antigen presentation may be useful as an anti- tumor treatment or to modulate the immune system.

As an agent to direct an individuals immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

As a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

As a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodificiency.

As a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect.

As a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence such as observed among SCID patients.

As an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

As a means of activating T cells.

As a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leshmania.

As pretreatment of bone marrow samples prior to transplant. Such treatment would increase B cell representation and thus accelerate recover.

As a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

Additionally, polypeptides or polynucleotides of the invention, and/or agonists thereof, may be used to treat or prevent IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema.

All of the above described applications as they may apply to veterinary medicine.

Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, or ribozymes. These would be expected to reverse many of the activities of the ligand described above as well as find clinical or practical application as:

A means of blocking various aspects of immune responses to foreign agents or self. Examples include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and pathogens.

A therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythramatosus and MS.

An inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

An inhibitor of graft versus host disease or transplant rejection.

A therapy for B cell and/or T cell malignancies such as ALL, Hodgkins disease, non-Hodgkins lymphoma, Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, and EBV-transformed diseases.

A therapy for chronic hypergammaglobulinemeia evident in such diseases as monoclonalgammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonalgammopathies, and plasmacytomas.

A therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

A means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

An immunosuppressive agent(s).

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

In another embodiment, administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention, may be used to treat or prevent IgE-mediated allergic reactions including, but not limited to, asthma, rhinitis, and eczema.

The agonists and antagonists may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

The agonists or antagonists may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain auto-immune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and

insulin-dependent diabetes. The antagonists or agonists may also be employed to treat infectious diseases including silicosis, sarcoidosis, idiopathic pulmonary fibrosis by, for example, preventing the recruitment and activation of mononuclear phagocytes. They may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration. The antagonists or agonists or may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

Antibodies against polypeptides of the invention may be employed to treat ARDS.

Agonists and/or antagonists of the invention also have uses in stimulating wound and tissue repair, stimulating angiogenesis, stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to treat or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carnii.

In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to treat, diagnose, and/or prevent (1) cancers or neoplasms and (2) autoimmune cell or tissue-related cancers or neoplasms. In a preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or

antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat, diagnose, and/or prevent acute myelogeneous leukemia. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat, diagnose, and/or prevent, chronic myelogeneous leukemia, multiple myeloma, non-Hodgkins lymphoma, and/or Hodgkins disease.

In another specific embodiment, polynucleotides or polypeptides, and/or agonists or antagonists of the invention may be used to treat, diagnose, prognose, and/or prevent selective IgA deficiency, myeloperoxidase deficiency, C2 deficiency, ataxia-telangiectasia, DiGeorge anomaly, common variable immunodeficiency (CVI), X-linked agammaglobulinemia, severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), and Wiskott-Aldrich syndrome.

Examples of autoimmune disorders that can be treated or detected are described above and also include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of

polynucleotides or polypeptides, or agonists or antagonists of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to modulate inflammation. For example, polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including chronic prostatitis, granulomatous prostatitis and malacoplakia, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prognosed, prevented, and/or diagnosed using antibodies against the polypeptide of the invention.

As an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

Additionally, polynucleotides, polypeptides, and/or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis

and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metastisis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren’s syndrome,

Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Hyperproliferative diseases and/or disorders that could be detected and/or treated by polynucleotides, polypeptides, and/or antagonists of the invention, include, but are not limited to neoplasms located in the: liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Hyperproliferative Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response.

Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by Polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the poynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferrably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present

invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragements thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragements thereof. Preferred binding affinities include those with a dissociation constant or Kd less than $5X10^{-6}M$, $10^{-6}M$, $5X10^{-7}M$, $10^{-7}M$, $5X10^{-8}M$, $10^{-8}M$, $5X10^{-9}M$, $10^{-9}M$, $5X10^{-10}M$, $10^{-10}M$, $5X10^{-11}M$, $10^{-11}M$, $5X10^{-12}M$, $10^{-12}M$, $5X10^{-13}M$, $10^{-13}M$, $5X10^{-14}M$, $10^{-14}M$, $5X10^{-15}M$, and $10^{-15}M$.

Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al., Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-

mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuviants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such thereapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodes associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodes of the invention may be associated with with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

Cardiovascular Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat cardiovascular disorders, including peripheral artery disease, such as limb ischemia.

Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects.

Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

Heart valve disease include aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis,

carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromoboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

Ischemia includes cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, are especially effective for the treatment of critical limb ischemia and coronary disease.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Anti-Angiogenesis Activity

The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al., Cell* *56*:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and

spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al., Biotech. 9*:630-634 (1991); Folkman *et al., N. Engl. J. Med., 333*:1757-1763 (1995); Auerbach *et al., J. Microvasc. Res. 29*:401-411 (1985); Folkman, Advances in Cancer Research, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Opthalmol. 94*:715-743 (1982); and Folkman *et al.,* Science *221*:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science 235*:442-447 (1987).

The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.,* Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)).Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non- small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered

topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also

provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al., Am. J. Ophthal. 85*:704-710 (1978) and Gartner *et al., Surv. Ophthal. 22*:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within

further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

Within particularly preferred embodiments of the invention, proliferative diabetic

retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreous injection and/or via intraocular implants.

Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

Moreover, disorders and/or states, which can be treated with be treated with the the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uvietis, delayed wound healing, endometriosis, vascluogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have

occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor. Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one

embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine

sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP-PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

Diseases at the Cellular Level

Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides,

polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren’s syndrome, Hashimoto’s thyroiditis, biliary cirrhosis, Behcet’s disease, Crohn’s disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host

disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associted with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as

agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intesting, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and doudenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflamamatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid

more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or

antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Neural Activity and Neurological Diseases

The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes

(diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful

according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, *10*:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, *70*:65-82 (1980), or Brown *et al.*, *Ann. Rev. Neurosci.*, *4*:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral

disorders include, but are not limited to, Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms,

canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningtitis such as viral meningtitis which includes lymphocytic choriomeningitis, Bacterial meningtitis which includes Haemophilus Meningtitis, Listeria Meningtitis, Meningococcal Meningtitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningtitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningtitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sceloris which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis,

transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucolipidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle

spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyloclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia,Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as

causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Infectious Disease

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E,

Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Cryptococcus neoformans, Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia (e.g., Borrelia burgdorferi, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, E. coli (e.g., Enterotoxigenic E. coli and Enterohemorrhagic E. coli), Enterobacteriaceae (Klebsiella, Salmonella (e.g., Salmonella typhi, and Salmonella paratyphi), Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Mycobacterium leprae, Vibrio cholerae, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Menigococcal), Meisseria meningitidis, Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus (e.g., Heamophilus influenza type B), Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, Shigella spp., Staphylococcal, Meningiococcal, Pneumococcal and Streptococcal (e.g., Streptococcus pneumoniae and Group B Streptococcus). These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme

Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis (e.g., mengitis types A and B), Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, Ppolynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, Diptheria, botulism, and/or meningitis type B.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., Plasmodium virax, Plasmodium falciparium, Plasmodium malariae and Plasmodium ovale). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to

repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associatedwith vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

Chemotaxis

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or

endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors),or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially

containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labelled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor

molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al., Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al., J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be alterred by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not

necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and 3[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of 3[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of 3[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a colon and/or colon cancer polynucleotides and/or polypeptides polypeptide

of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a colon and/or colon cancer polynucleotides and/or polypeptides polypeptide of the invention, (b) assaying a biological activity , and (b) determining if a biological activity of the polypeptide has been altered.

Colon Cancer Antigen Binding Peptides and Other Molecules

The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind the colon cancer antigens of the invention, and the colon cancer antigen binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the colon cancer antigens of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

This method comprises the steps of:

a. contacting a colon cancer antigen of the invention with a plurality of molecules; and

b. identifying a molecule that binds the colon cancer antigen.

The step of contacting the colon cancer antigen of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the colon cancer antigen on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized colon cancer antigen. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized colon cancer antigen of the invention. The molecules having a selective affinity for the colon cancer antigen can then be purified by affinity selection. The nature of the solid support, process for attachment of the colon cancer antigen of the invention to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be

expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by a colon cancer antigen, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the colon cancer antigen and the individual clone. Prior to contacting the colon cancer antigen of the invention with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for protein of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for a colon cancer antigen of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

In certain situations, it may be desirable to wash away any unbound colon cancer antigen, or alterntatively, unbound polypeptides, from a mixture of the colon cancer antigen of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the protein of the invention or the plurality of polypeptides is bound to a solid support.

The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind to a protein of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, Science 251:767-773; Houghten et al., 1991, Nature 354:84-86; Lam et al., 1991, Nature 354:82-84; Medynski, 1994, Bio/Technology 12:709-710;Gallop et al., 1994, J. Medicinal Chemistry 37(9):1233-1251; Ohlmeyer et al., 1993, Proc. Natl. Acad. Sci. USA 90:10922-10926; Erb et al., 1994, Proc. Natl. Acad. Sci. USA 91:11422-11426; Houghten et al., 1992, Biotechniques 13:412; Jayawickreme et al., 1994, Proc. Natl. Acad. Sci. USA 91:1614-1618; Salmon et al., 1993,

Proc. Natl. Acad. Sci. USA 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381-5383.

Examples of phage display libraries are described in Scott and Smith, 1990, Science 249:386-390; Devlin et al., 1990, Science, 249:404-406; Christian, R. B., et al., 1992, J. Mol. Biol. 227:711-718); Lenstra, 1992, J. Immunol. Meth. 152:149-157; Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

In vitro translation-based libraries include, but are not limited to, those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one

monomer, giving the libraries added flexibility.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, Science 249:386-390; Fowlkes et al., 1992; BioTechniques 13:422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89:5393-5397; Yu et al., 1994, Cell 76:933-945; Staudt et al., 1988, Science 241:577-580; Bock et al., 1992, Nature 355:564-566; Tuerk et al., 1992, Proc. Natl. Acad. Sci. USA 89:6988-6992; Ellington et al., 1992, Nature 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, Science 263:671-673; and CT Publication No. WO 94/18318.

In a specific embodiment, screening to identify a molecule that binds a colon cancer antigen can be carried out by contacting the library members with a colon cancer antigen of the invention immobilized on a solid phase and harvesting those library members that bind to the colon cancer antigen. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes et al., 1992, BioTechniques 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to a colon and/or colon cancer related protein of the invention.

Where a colon cancer antigen of the invention binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can

be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

As mentioned above, in the case of a colon and/or colon cancer related protein of the invention binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a colon and/or colon cancer related protein of the invention binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

The selected colon cancer antigen protein of the invention binding polypeptide can be obtained by chemical synthesis or recombinant expression.

Targeted Delivery

In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a colon cancer antigen of the invention.

As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

Drug Screening

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Antisense And Ribozyme (Antagonists)

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained in the deposited clone identified in Table 1. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of

Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoR1 site on the 5 end and a HindIII site on the 3 end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl2, 10MM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the

art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invnetion or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster, et al., Nature 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of shown in Table 1 could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region

of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of

SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.
The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

The antagonist/agonist may also be employed to treat the diseases described herein.
Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

Other Activities

A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in

treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier in Table 2.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in a cDNA library shown in Table 9 which was

deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier in Table 2.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Id in Table 1 which DNA molecule is contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a protein identified in Table 1, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the

group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300, 500, 1000, 2000, 3000 or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete

amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier in Table 2.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was

deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an

amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Protein of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Protein of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in a cDNA library shown in Table 9 which was deposited with the American Type Culture Collection and given the ATCC Deposit Numbers shown above for said cDNA library identifier.

Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a specific delivery of toxic compositions to diseased cells (e.g., including, but not limited to, colon or colon cancer cells or tissues), which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide of the invention, including, but not limited to a binding agent, or antibody of the claimed invention that are associated with toxin or cytotoxic prodrugs.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 9 identifies the vectors used to construct the cDNA library from which each clone was isolated.

Table 9.

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HASA	Uni-ZAP XR	LP03
HFCA HFCD HFCE HFCF	Uni-ZAP XR	LP13
HFKF	Uni-ZAP XR	LP13
HE8A HE8B HE8C HE8D HE8E HE8F HE8N HE8O HE8P HE8Q HE8T HE8U	Uni-ZAP XR	LP03
HGBA HGBG HGBH	Uni-ZAP XR	LP13
HGBB	Uni-ZAP XR	LP03
HHFA	pBluescript	NA
HLHA HLHB HLHC HLHD HLHE HLHG	Uni-ZAP XR	LP03
HOOA	pBluescript	NA
HPLB	Uni-ZAP XR	NA
HPMD HPME HPMF	Uni-ZAP XR	LP03
HPRA	Uni-ZAP XR	LP13
HSIA HSIC HSID HSIE	Uni-ZAP XR	LP03
HTEA HTEB HTEC HTED HTEE HTEF HTEG HTEH HTEJ HTEK	Uni-ZAP XR	LP13
HTPA HTPC	Uni-ZAP XR	LP03
HTTB HTTC HTTD HTTE HTTF	Uni-ZAP XR	LP13
HAPA HAPC	Uni-ZAP XR	LP03
HETA HETB HETC HETD HETG HETH HETI HETJ	Uni-ZAP XR	LP03
HHFB HHFC HHFG HHFH HHFI	Uni-ZAP XR	LP13
HHPE HHPG	Uni-ZAP XR	LP03
HCE1 HCE2 HCE3 HCE4 HCEC HCED HCEE HCEF HCEI HCEM HCEN HCEO HCEP	Uni-ZAP XR	LP03
HUVC HUVD	Uni-ZAP XR	LP13
HUKB HUKF	Lamda ZAP II	LP13
HTHC HTHD	Uni-ZAP XR	LP13
HSTA	Uni-ZAP XR	LP13
HTAE	Uni-ZAP XR	LP13
HLEA	Uni-ZAP XR	PA005 Phage
HFEA HFEB	Uni-ZAP XR	LP13
HJPA HJPC	Uni-ZAP XR	LP13
HCNA	Lambda ZAP II	LP01
HTSG	pBS	LP05
HLTA HLTB HLTC HLTD HLTE	Uni-ZAP XR	LP03
HAHS	pBluescript	LP13
HALS	Uni-ZAP XR	LP13
HE6B HE6F HE6G	Uni-ZAP XR	LP04
HF6S	pBluescript	LP13
HPMS	pBluescript	LP03
HTYS	pBluescript	NA
HRDB HRDD HRDE HRDF	Uni-ZAP XR	LP03
HCAB	Uni-ZAP XR	LP13
HL3A	Uni-ZAP XR	PA005 Phage
HRGD	Uni-ZAP XR	LP13
HSSE HSSG HSSJ	Uni-ZAP XR	LP04
HSUA HSUB	Uni-ZAP XR	LP03
HT3A	Uni-ZAP XR	NA

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HT4C	Uni-ZAP XR	LP03
HE9F HE9H HE9M HE9N HE9O HE9P HE9Q HE9R HE9S HE9T	Uni-ZAP XR	LP13
HEPA HEPB	Uni-ZAP XR	LP04
HSFA	Uni-ZAP XR	LP13
HATA HATB HATC HATE	Uni-ZAP XR	LP13
HT3B	Uni-ZAP XR	PA005 Phage
HSNA	Uni-ZAP XR	LP04
HPFC	Uni-ZAP XR	LP04
HE2A HE2D HE2E HE2H HE2I HE2O	Uni-ZAP XR	LP13
HE2B HE2C HE2F HE2P	Uni-ZAP XR	LP13
HCBB	Uni-ZAP XR	NA
HFGA	Uni-ZAP XR	LP03
HNEA HNED	Uni-ZAP XR	LP13
HBGB	Uni-ZAP XR	LP03
HKCA	Uni-ZAP XR	PA005 Phage
HKLA	Lambda ZAP II	PA005 Phage
HBNA	Uni-ZAP XR	LP03
HCET	pBluescript	PA005 Phage
HKCS HKCU	pBluescript	LP03
HKCT	pBluescript	PA005 Phage
HL1S	pBluescript	LP13
HLHS HLHT	pBluescript	LP13
HPRT	pBluescript	PA005 Phage
HPTT	Uni-ZAP XR	LP13
HRGS	pBluescript	LP03
HSUS	pBluescript	LP13
HT2S	Uni-ZAP XR	NA
HCNS	pBluescript	PA005 Phage
HCNU	pBluescript	PA005 Phage
HKLR	pBluescript	PA005 Phage
HKLS	pBluescript	PA005 Phage
HKTA	Uni-ZAP XR	PA005 Phage
HHFU	pBluescript	NA
HE8S	Uni-ZAP XR	LP03
HCDC HCDE	Uni-ZAP XR	LP03
HOAA	Uni-ZAP XR	LP13
HTLA HTLD HTLE	Uni-ZAP XR	LP03
HLMD	Uni-ZAP XR	PA005 Phage
HLMI HLMM	Lambda Zap II	LP01

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
H6EA H6EB	Uni-ZAP XR	LP03
HCEV HCEY	Uni-ZAP XR	LP03
HCQA HCQB	Lambda Zap II	LP01
HTOA HTOD HTOH HTOJ	Uni-ZAP XR	LP13
HTXC HTXF	Uni-ZAP XR	LP03
HMEC HMEE HMEG HMEI HMEK	Lambda Zap II	LP01
HMEB	Lambda Zap II	LP13
HNFE HNFF HNFG HNFH	Uni-ZAP XR	LP03
HKEA	ZAP express	PA005 Phage
HMGB	Uni-ZAP XR	LP13
HMHB	Uni-ZAP XR	PA005 Phage
HAUA HAUB	Uni-ZAP XR	LP13
HAQB	Uni-ZAP XR	LP13
HCWH	ZAP express	LP02
HCUC	ZAP express	LP02
HSVB HSVC	Uni-ZAP XR	LP03
HPXA	pBluescript	NA
HBJE HBJF HBJJ HBJM	Uni-ZAP XR	LP13
HCRB	Uni-ZAP XR	LP03
HODA HODB HODC HODD	Uni-ZAP XR	LP13
HDSA	Uni-ZAP XR	LP03
HLQA HLQB	Lambda Zap II	LP01
HHGC HHGD	Lambda Zap II	LP01
HCPA	Uni-ZAP XR	LP13
HMWA HMWB HMWD HMWF HMWH HMWI	Uni-ZAP XR	LP03
HERA	Uni-ZAP XR	LP13
HGLA	Uni-ZAP XR	LP13
HWTB HWTC	Uni-ZAP XR	LP13
HLLC	pCMVSport1	PA005 DNA
HLIB HLIC	pCMVSport1	LP12
HKDB	pCMVSport1	NA
HRKA	pBluescript	PA005 Phage
HOSX	pBluescript	PA005 Phage
HEAA	Uni-ZAP XR	LP13
HBCB HBCC	Uni-ZAP XR	LP21
HHBE HHBF HHBH	pCMVSport1	LP12
HBBB	pCMVSport1	LP12
HLJB HLJD HLJE	pCMVSport1	LP12
HSEB	pCMVSport1	NA
HNAA	pSport1	NA
HBSA	Uni-ZAP XR	LP04
HBBM	pCMVSport1	NA
HADM	pBluescript	NA
HMKA HMKC	pSport1	LP12
HFVH HFVI HFVJ HFVK	pBluescript	LP03
HKIM	Lambda Zap II	PA005 Phage

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HCUD HCUE HCUG	ZAP express	LP02
HKIS	pBluescript	NA
HSDS	pBluescript	LP13
HBAG HBAH	pSport1	NA
HUSG HUSI HUSJ	pSport1	LP10
HUSX HUSY HUSZ	pSport1	LP10
HOFM	pCMVSport 2.0	LP07
HNFI	pBluescript	LP03
HBMC HBMD	pBluescript	LP03
HCFB HCFC HCFD	pSport1	LP12
HCFL HCFM HCFN HCFO	pSport1	LP12
HPTW	pBluescript	PA005 Phage
HADC HADF	pSport1	LP10
HOVA HOVC HOVD HOVE	pSport1	LP10
HKML HKMM	pBluescript	LP03
HUSF	pBluescript	NA
HOGA HOGB HOGC HOGD HOGE	pCMVSport 2.0	LP12
HTWB HTWC HTWD HTWE HTWF	pSport1	LP10
HBXF	ZAP express	LP02
HEOA	pBluescript	PA005 DNA
HSDX	pBluescript	LP13
HMMA	pSport1	LP12
HLYA HLYB HLYC HLYD HLYE HLYG	pSport1	LP10
HCGL	pCMVSport 2.0	LP07
HSDZ	pBluescript	LP13
HEON HEOQ HEOS	pSport1	LP10
HCGB	pSport1	LP10
HADT	pBluescript	NA
HTDA	pSport1	LP12
HSPA HSPB	pSport1	LP10
HSPM	pSport1	LP10
HCHA HCHB HCHC	pSport1	LP10
HCHM HCHO	pSport1	LP10
HDLA	pCMVSport 2.0	LP07
HDTA HDTB HDTD HDTE HDTG HDTH HDTI HDTJ HDTK HDTL HDTM	pCMVSport 2.0	LP07
HTJM HTJN	pCMVSport 2.0	LP12
HCIA	pSport1	LP10
H6BS	Uni-ZAP XR	LP03
HKAA HKAB HKAC HKAD HKAE HKAF HKAH HKAJ HKAK HKAO	pCMVSport 2.0	LP07
HDAA HDAB HDAC	pSport1	LP10
HUFA HUFB HUFC HUFD HUFF	pSport1	LP10
HLDB HLDC HLDD	pCMVSport 3.0	LP08

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HLDN HLDO	pCMVSport 3.0	LP08
HNDA	pCMVSport 2.0	LP07
HMTA HMTB	pCMVSport 3.0	LP08
HNTA HNTB HNTC HNTD HNTE	pCMVSport 3.0	LP08
HNTM	pSport1	LP10
HDPA HDPB HDPC HDPF HDPG HDPH HDPI HDPJ HDPK HDPL HDPR HDPS HDPT HDPU HDPW HDPX HDQD HDQE HDQF HDQG HDQH	pCMVSport 3.0	LP08
HDPM HDPO HDPP HDPQ HDQP	pCMVSport 3.0	LP08
HMTM	PCRII	LP09
HLDX	pSport1	LP10
HMUB	pCMVSport 3.0	LP08
HULA HULC	pSport1	LP10
HFNA	pSport1	LP10
HKGA HKGB HKGC HKGD	pSport1	LP10
HISA HISB HISC HISD HISE	pSport1	LP10
HLSA	pSport1	LP10
HHEA HHEB HHEC HHED HHEE HHEF HHEG HHEH HHEI HHEJ	pCMVSport 3.0	LP08
HHEM HHEN HHEP HHEQ HHER HHET HHEU HHEV HHEW HHEX HHEY HHEZ	pCMVSport 3.0	LP08
HEQA	pCMVSport 3.0	LP08
HJMA HJMB	pCMVSport 3.0	LP08
HSWB	pCMVSport 3.0	LP08
HNTR HNTS HNTT	pSport1	NA
HEEA	Uni-ZAP XR	NA
HEGA	Uni-ZAP XR	NA
HSYA HSYB HSYD HSYE	pCMVSport 3.0	LP08
HLWA HLWB HLWC	pCMVSport 3.0	LP08
HRAA HRAB HRAC HRAE	pCMVSport 3.0	LP08
HTXJ HTXK HTXL HTXM HTXO HTXP HTXQ HTXR HTXS	Uni-ZAP XR	LP03
H6ED	Uni-ZAP XR	LP03
HAMF HAMG	pCMVSport 3.0	LP12
HAJA HAJB	pCMVSport 3.0	LP12
HDFU	pCMVSport 2.0	NA
HDHE	pCMVSport 2.0	NA
HLQD HLQE HLQF	Lamda ZAP II	LP13

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HAPN HAPO HAPQ HAPR	Uni-ZAP XR	LP13
HWBA HWBB HWBC HWBD HWBE HWBF	pCMVSport 3.0	LP12
HWAA HWAB HWAC HWAD HWAG HWAI	pCMVSport 3.0	LP12
HYAA HYAB HYAC	pCMVSport 3.0	LP12
HWHG HWHH	pCMVSport 3.0	LP12
HWHP HWHQ	pCMVSport 3.0	LP12
HCWU	ZAP Exress	LP13
HSIF HSIG	Uni-ZAP XR	PA005 Phage
HLTG HLTH HLTI	Uni-ZAP XR	LP13
HARM HARN	pCMVSport 3.0	LP12
HBIM HBIN HBIO HBIP	pCMVSport 3.0	LP12
HSOB HSOD	Uni-ZAP XR	LP03
HCQC HCQD	Lambda ZAP II	LP01
HCNC HCND	Lambda ZAP II	LP01
HROB HROD	Uni-ZAP XR	LP03
HAHC	Uni-ZAP XR	LP13
HWDA	pCMVSport 3.0	LP12
HODE HODF HODG	Uni-ZAP XR	LP03
HTEL HTEP	Uni-ZAP XR	LP03
HBGM HBGN	Uni-ZAP XR	LP03
HTLG HTLH	Uni-ZAP XR	LP03
HHFJ HHFL HHFM	Uni-ZAP XR	LP03
HFKH HFKI HFKM	Uni-ZAP XR	LP03
HTPF HTPG HTPH HTPI	Uni-ZAP XR	LP03
HUVF HUVG HUVH	Uni-ZAP XR	LP03
HE2J HE2L HE2R HE2T	Uni-ZAP XR	LP04
HS2A	pSport1	LP16
HS2S	pSport1	LP16
HLQG	Lambda Zap II	LP01
HA5A HA5B	pSport1	LP16
HTTI HTTK	Uni-ZAP XR	LP03
HTAH	Uni-ZAP XR	LP03
HDDN	pSport1	LP22
HPCI	Lambda Zap-CMV XR	LP21
HPCR	Lambda Zap-CMV XR	LP22
HPMK HPML	Uni-ZAP XR	LP03
HHFO	Uni-ZAP XR	LP03
HAAA	pSport1	LP22
HOOH	pSport1	LP22
HIDA	pSport1	LP22
HNOA	pSport1	LP22

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HUUA	pTrip1Ex2	LP22
HPDO	pSport1	PA005 DNA
HPCO	pSport1	PA005 DNA
HOCM	pSport1	PA005 DNA
HNBT	pSport1	PA005 DNA
HBCJ	pSport1	PA005 DNA
HSAM	pSport1	PA005 DNA
HFXA HFXH	Lambda ZAP II	LP01
HMSA HMSC HMSD HMSF HMSG HMSH HMSI HMSJ	Uni-ZAP XR	LP03
HOSA HOSB HOSD HOSM HOSN HOSO HOSP	Uni ZAP XR	LP04
HEBA HEBB HEBF HEBG	Uni ZAP XR	NA
HAGB HAGD HAGE HAGF	Uni-ZAP XR	LP13
HSRA HSRB	Uni-ZAP XR	LP03
HPVA	Uni ZAP XR	PA005 Phage
HKIA	Uni ZAP XR	PA005 Phage
HKMA	Uni ZAP XR	NA
HSRF	Uni-ZAP XR	LP03
HSQD HSQF	Uni-ZAP XR	LP03
HSKE HSKZ	Uni-ZAP XR	LP03
HSLE HSLF HSLG HSLH	Uni-ZAP XR	LP03
HSDE HSDH	Uni-ZAP XR	LP03
HSXA HSXB HSXD	Uni-ZAP XR	LP04
HSHA HSHB	Uni-ZAP XR	LP13
HBXA HBXB HBXC	ZAP Express	LP13
HOUA HOUD	Uni-ZAP XR	LP04
HPWA HPWB HPWC	Uni-ZAP XR	LP13
HELB HELG HELH	Uni-ZAP XR	LP04
HEMF HEMG	Uni-ZAP XR	LP04
HBIB	Uni-ZAP XR	LP04
HFRA HFRB	Uni ZAP XR	PA005 Phage
HHSB HHSD	Uni-ZAP XR	LP04
HNGB HNGE HNGG HNGI	Uni-ZAP XR	LP04
HNHD HNHE HNHH	Uni-ZAP XR	LP04
HADB	Uni ZAP XR	NA
HSAV HSAW HSAX HSAZ	Uni-ZAP XR	LP04
HBMS HBMT HBMV HBMX	Uni-ZAP XR	LP04
HOBA	pBluescript	PA005 Phage
HOEE HOEF HOEK HOEL HOEM HOEN HOEO	Uni ZAP XR	PA005 Phage
HAIB HAIC HAID	Uni-ZAP XR	LP04
HTGA HTGB	Uni-ZAP XR	LP04
HEIB HEIC	Uni ZAP XR	NA

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
HMCD	Uni-ZAP XR	LP04
HPCA	Uni ZAP XR	NA
HPHA	Uni-ZAP XR	LP04
HPIA HPIC	Uni-ZAP XR	LP13
HPJA HPJB HPJC HPJE	Uni-ZAP XR	LP13
HFIA HFIB HFIC	pSport1	LP10
HFIH HFII HFIJ	pSport1	LP10
HFIU	pSport1	LP10
HSKX	pBluescript	LP03
HGCO	pSport1	NA
HMVA HMVB HMVC HMVD	pSport1	LP10
HOSE HOSF	Uni-ZAP XR	LP04
HNHN HNHO	Uni ZAP XR	LP04
HTGE HTGF	Uni-ZAP XR	LP04
HFPB HFPC HFPE HFPF HFPH HFPI HFPJ HFPK	Uni-ZAP XR	LP03
HFIX HFIY HFIZ	pSport1	LP10
HOHA HOHB HOHC HOHE	pCMVSport 2.0	LP07
HSDJ HSDK	Uni-ZAP XR	LP03
HFOX HFOY	pSport1	LP10
HMAH HMAJ HMAK HMAM	Uni-ZAP XR	LP04
HACB HACC	Uni-ZAP XR	LP04
HFXK	Lambda ZAP II	PA005 Phage
HFAT	Uni ZAP XR	PA005 Phage
HANG	pSport1	NA
HOUH	Uni ZAP XR	NA
HMCF HMCG HMCH HMCI	Uni-ZAP XR	LP13
HWLE HWLF HWLG HWLH HWMA	pSport1	LP14
HCRM HCRN HCRO HCRP HCRQ	pSport1	LP14
HWLI HWLJ HWLK HWLL HWMF	pSport1	LP14
HWLQ HWLR HWLU HWLV HWLW HWLX	pSport1	LP14
HBOD HBOE	pSport1	LP14
HBKD	pSport1	LP14
HWLA HWLC HWLD HWLP	pSport1	LP14
HWLM HWLN HWLO HWMB HWMC	pSport1	LP14
HVAA	pSport1	LP12
HBWC	ZAP express	LP13
HHSF HHSG	Uni ZAP XR	LP04
HSLJ	Uni ZAP XR	NA
HAQN	pSport1	LP14
HASM	pSport1	LP14
HCDM	pSport1	LP14
HFDM	pSport1	LP14
HGAM	pSport1	LP14
HHMM	pSport1	LP14
HAVM	pT-Adv	LP14
HAVT	pT-Adv	LP14
HHAT HHAU	pT-Adv	LP14
HUCN HUCO HUCP HUCQ	pSport1	LP20
HHAO	pCMVSport	LP15

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
	3.0	
HTFN	pSport1	LP16
HMSM HMSO HMSP	Uni ZAP XR	PA005 Phage
HEPN	pSport1	LP20
HPSN	pSport1	LP20
HNSA	pSport1	LP20
HNSM	pSport1	LP20
HOCN	pSport1	LP20
HOCT	pSport1	LP20
HLXN	pSport1	LP20
HTYN	pSport1	LP20
HZAA	pSport1	LP20
HINA	pSport1	LP16
HRMA	pSport1	LP16
HSKI HSKJ HSKK	pBluescript	LP03
HACA	Uni-ZAP XR	LP13
HFAA HFAC HFAD	Uni-ZAP XR	LP04
HFAM	Uni-ZAP XR	LP04
HMIA HMIB	Uni-ZAP XR	LP04
HILB HILC	pBluescript SK-	PA005 Phage
HPBE	pBluescript SK-	LP13
HIBC HIBE	Other	NA
HPDD	pBluescript SK-	NA
HSAA HSAB HSAC	pBluescript	LP05
HSBA	pBluescript SK-	LP13
HJAA HJAC	pBluescript SK-	LP13
HJBA HJBC	pBluescript SK-	LP13
HAFB	pBS	LP05
HTNA HTNB	pBluescript SK-	LP13
HONA	pBluescript	LP05
HBMA	pBluescript SK-	NA
HARA	pBluescript	LP05
H2CA	pBluescript SK-	NA
H2MA	pBluescript SK-	NA
H2MB H2MC	pBluescript SK-	PA005 Phage
H2CB	pBluescript SK-	PA005 Phage
HCYA	pBluescript SK-	NA
HCYB	pBluescript	PA005

LIBRARIES DEPOSITED	VECTOR	ATCC DEPOSIT NO.
	SK-	Phage
H2LA H2LB	pBluescript SK-	PA005 Phage

In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

Vector Used to Construct Library	Corresponding Deposited Plasmid
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA
pSport1	pSport1
pCMVSport 2.0	pCMVSport 2.0
pCMVSport 3.0	pCMVSport 3.0
pCR®2.1	pCR®2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).)

Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 2 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 2 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that library in Table 2 and 9. First, a plasmid is directly isolated by screening the libraries using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring

Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 µl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 µM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of

the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue specific expression analysis

The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue specific cDNA libraries. Libraries generated from a particular tissue (e.g., those shown in Table 3 and 5) are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs which are predicted to have significantly enhances expression in colon or colon cancer tissues were selected.

The original clone from which the specific EST sequence was generated, is obtained from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured then transferred in 96 well format to a nylon membrane (Schleicher and Scheull) generating an array filter of colon and/or colon cancer related clones. Housekeeping genes, maize genes, known tissue specific genes and known membrane localized class I genes are included on the filters as controls. These targets can be used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed. The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuji phosphorimager.

Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified and the full length sequence of these clones is generated.

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial

expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Ampr), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kanr). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.^{600}) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500

mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4^{o} C or frozen at -80^{o} C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

The following alternative method can be used to purify a polypeptide expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by

weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 μm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH

6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 μg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce a colon or colon cancer related polypeptide, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., “A Manual of Methods for Baculovirus Vectors and

Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five µg of a plasmid containing the polynucleotide is co-transfected with 1.0 µg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One µg of BaculoGold™ virus DNA and 5 µg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 µl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 µl Lipofectin plus 90 µl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by

Life Technologies Inc., Gaithersburg, page 9- 10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of ^{35}S-methionine and 5 µCi ^{35}S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and

pCMVSport 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the colon or colon cancer related polypeptide, the vector does not need a second signal peptide.

Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five µg of the expression plasmid pC6 or pC4 is cotransfected with 0.5 µg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of metothrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 µM, 2 µM, 5 µM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 µM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al.,

Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the colon or colon cancer related polypeptide, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCCCAG
CACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGA
CACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGC
CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT
AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTC
AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAAGCC

AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAG
CTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGC
GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGAC
CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACC
GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT
GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT
GAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:8555)

Example 10: Production of an Antibody from a Polypeptide

a) Hybridoma Technology

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide of the present invention are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide of the present invention or, more preferably, with a secreted polypeptide of the present invention-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 μg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available

from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide of the present invention.

Alternatively, additional antibodies capable of binding to polypeptide of the present invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide of the present invention-specific antibody can be blocked by polypeptide of the present invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide of the present invention-specific antibody and are used to immunize an animal to induce formation of further polypeptide of the present invention-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

b) Isolation Of Antibody Fragments Directed Against Polypeptide of the Present Invention From A Library Of scFvs

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide of the present invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

Rescue of the Library. A library of scFvs is constructed from the RNA of human

PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 109 E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 μg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to innoculate 50 ml of 2xTY-AMP-GLU, 2 x 108 TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 μg/ml ampicillin and 50 ug/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 μg ampicillin/ml and 25 μg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 μm filter (Minisart NML; Sartorius) to give a final concentration of approximately 1013 transducing units/ml (ampicillin-resistant clones).

Panning of the Library. Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 μg/ml or 10 μg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 1013 TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1%

glucose and 100 μg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States

Biochemical). . Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Manheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 13: Formulation

The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant a polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given

continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Therapeutics can be are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate,

succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention

include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diptheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited

to, soluble forms of TNF-alpha, lymphotoxin- alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), TR6 (International Publication No. WO 98/30694), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892),TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not

limited to, TRIMETHOPRIM- SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the

Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

Conventional nonspecific immunosuppressive agents, that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

In specific embodiments, Therapeutics of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the Therapeutics of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucorticosteroids, and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

In an additional embodiment, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid

derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In another embodiment, compostions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephalen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

In a specific embodiment, Therapeutics of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, Therapeutics of the invention are administered in combination with Rituximab. In a further embodiment, Therapeutics of the invention are administered with Rituxmab and CHOP, or Rituxmab and any combination of the components of CHOP.

In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not

limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL- 4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PIGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PIGF-2), as disclosed in Hauser et al., Gorwth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are incorporated herein by reference herein.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

Example 14: Method of Treating Decreased Levels of the Polypeptide

The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a colon or colon cancer related polypeptide in an individual can be treated by administering the agonist or antagonist of the present invention. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the agonist or antagonist to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the agonist or antagonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 13.

Example 15: Method of Treating Increased Levels of the Polypeptide

The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day

for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 13.

Example 16: Method of Treatment Using Gene Therapy-Ex Vivo

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention

Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA,* 86:8932-8935 (1989); and Zijlstra et al., *Nature,* 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous

polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na_2HPO_4, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin.

The final cell suspension contains approximately $3X10^6$ cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3'end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3'end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5'end and a HindIII site at the 3'end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 μg/ml. 0.5 ml of the cell suspension (containing approximately $1.5.X10^6$ cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 μF and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 18: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus,

heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal

injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 19: Transgenic Animals

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989));

electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.,* mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.,* head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration

of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 20: Knock-Out Animals

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect

cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 21: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation

Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the

detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

In Vitro Assay- Agonists or antagonists of the invention can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the agonists or antagonists of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed Staphylococcus aureus Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added 10^5 B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5 X 10^{-5}M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and 10^{-5} dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with 3H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

In Vivo Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of agonists or antagonists of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with agonists or antagonists of the invention identify the results of the activity of the agonists or antagonists on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with agonist or antagonist is used to indicate whether the agonists or antagonists specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and agonists or antagonists-treated mice.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 22: T Cell Proliferation Assay

A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ^{3}H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 μl/well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1 μg/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x 10^4/well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of agonists or antagonists of the invention (total volume 200 ul). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100 μl of supernatant is removed and stored –20 degrees C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 ul of medium containing 0.5 uCi of ^{3}H-thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of ^{3}H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of agonists or antagonists of the invention.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 23: Effect of Agonists or Antagonists of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells

Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF-α, causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FCγRII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of agonist or antagonist of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Thl helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells (10^6/ml) are treated with increasing concentrations of agonists or antagonists of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e..g, R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of agonists or antagonists of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Agonists or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of 2 x 10^6/ml in PBS containing PI at a

final concentration of 5 μg/ml, and then incubaed at room temperature for 5 minutes before FACScan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of $5x10^5$ cells/ml with increasing concentrations of agonists or antagonists of the invention and under the same conditions, but in the absence of agonists or antagonists. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of agonist or antagonist of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e. g, R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

Oxidative burst. Purified monocytes are plated in 96-w plate at $2\text{-}1x10^5$ cell/well. Increasing concentrations of agonists or antagonists of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 μl 1N NaOH per well. The absorbance is read at 610 nm. To calculate the amount of H_2O_2 produced by the macrophages, a standard curve of a H_2O_2 solution of known molarity is performed for each experiment.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 24: Biological Effects of Agonists or Antagonists of the Invention

Astrocyte and Neuronal Assays.

Agonists or antagonists of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an agonist or antagonist of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA 83*:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of an agonist or antagonist of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

Fibroblast and endothelial cell assays.

Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is

added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE_2 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or agonists or antagonists of the invention with or without IL-1α for 24 hours. The supernatants are collected and assayed for PGE_2 by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without agonists or antagonists of the invention IL-1α for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or agonists or antagonists of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with agonists or antagonists of the invention.

Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP^+) and released. Subsequently, MPP^+ is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP^+ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotidamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

Based on the data with FGF-2, agonists or antagonists of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an agonist or antagonist of the invention is first examined in vitro in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm^2 on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days in vitro and are processed for tyrosine hydroxylase, a specific marker for dopminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if an agonist or antagonist of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the agonist or antagonist may be involved in Parkinson's Disease.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 25: The Effect of Agonists or Antagonists of the Invention on the Growth of Vascular Endothelial Cells

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at 2-5x10^4 cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnique,

Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An agonist or antagonist of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

An increase in the number of HUVEC cells indicates that the compound of the invention may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cell indicates that the compound of the invention inhibits vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 26: Rat Corneal Wound Healing Model

This animal model shows the effect of an agonist or antagonist of the invention on neovascularization. The experimental protocol includes:

a) Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.

b) Inserting a spatula below the lip of the incision facing the outer corner of the eye.

c) Making a pocket (its base is 1-1.5 mm form the edge of the eye).

d) Positioning a pellet, containing 50ng- 5ug of an agonist or antagonist of the invention, within the pocket.

e) Treatment with an agonist or antagonist of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 27: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models

A. Diabetic db+/db+ Mouse Model.

To demonstrate that an agonist or antagonist of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al., J. Surg. Res. 52*:389 (1992); Greenhalgh, D.G. *et al., Am. J. Pathol. 136*:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al. Proc. Natl. Acad. Sci. USA 77*:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al., J. Immunol. 120*:1375 (1978); Debray-Sachs, M. *et al., Clin. Exp. Immunol. 51(1)*:1-7 (1983); Leiter *et al., Am. J. of Pathol. 114*:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al., Exp. Neurol. 83(2)*:221-232 (1984); Robertson *et al., Diabetes 29(1)*:60-67 (1980); Giacomelli *et al., Lab Invest. 40(4)*:460-473 (1979); Coleman, D.L., *Diabetes 31 (Suppl)*:1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al., J. Immunol. 120*:1375-1377 (1978)).

The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al., Am. J. of Pathol. 136*:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the

rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med. 172*:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

An agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is $64mm^2$, the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an agonist or antagonist of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al., Am. J. Pathol. 136:*1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

B. Steroid Impaired Rat Model

The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl*et al., J. Immunol. 115*: 476-481 (1975); Werb *et al., J. Exp. Med. 147*:1684-1694 (1978)). Glucocorticoids retard

wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *An. Intern. Med. 37*:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*, *Growth Factors. 5:* 295-304 (1991); Haynes *et al.*, *J. Clin. Invest. 61:* 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes et al., *J. Clin. Invest. 61:* 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In:* Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al.*, *Growth Factors. 5:* 295-304 (1991); Haynes *et al.*, *J. Clin. Invest. 61:* 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In*: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al.*, *Proc. Natl. Acad. Sci. USA 86*: 2229-2233 (1989)).

To demonstrate that an agonist or antagonist of the invention can accelerate the healing process, the effects of multiple topical applications of the agonist or antagonist on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

The agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is $64mm^2$, the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with an agonist or antagonist of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 28: Lymphadema Animal Model

The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of an agonist or antagonist of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of dye into paws.

Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

Using a microscope, muscles in back of the leg (near the semitendinosis and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and Ca2+ comparison.

Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold

methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 29: Suppression of TNF alpha-induced adhesion molecule expression by a Agonist or Antagonist of the Invention

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Tumor necrosis factor alpha (TNF-a), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of an agonist or antagonist of the invention to mediate a suppression of TNF-a induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF-a treated ECs when co-stimulated with a member of the FGF family of proteins.

To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO2. HUVECs are seeded in 96-well plates at concentrations of 1 x 104 cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution

of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 ul of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 ul volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 µl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 µl of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 µg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20 µl of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNNP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 30: TAQMAN

Quantitative PCR (QPCR). Total RNA from cells in culture are extracted by Trizol separation as recommended by the supplier (LifeTechnologies). (Total RNA is treated with DNase I (Life Technologies) to remove any contaminating genomic DNA before reverse transcription.) Total RNA (50 ng) is used in a one-step, 50ul, RT-QPCR, consisting of Taqman Buffer A (Perkin-Elmer; 50 mM KCl/10 mM Tris, pH 8.3), 5.5 mM $MgCl_2$, 240 μM each dNTP, 0.4 units RNase inhibitor(Promega), 8%glycerol, 0.012% Tween-20, 0.05% gelatin, 0.3uM primers, 0.1uM probe, 0.025units Amplitaq Gold (Perkin-Elmer) and 2.5 units Superscript II reverse transcriptase (Life Technologies). As a control for genomic contamination, parallel reactions are setup without reverse transcriptase. The relative abundance of (unknown) and 18S RNAs are assessed by using the Applied Biosystems Prism 7700 Sequence Detection System (Livak, K. J., Flood, S. J., Marmaro, J., Giusti, W. & Deetz, K. (1995) PCR Methods Appl. 4, 357-362). Reactions are carried out at 48°C for 30 min, 95°C for 10 min, followed by 40 cycles of 95°C for 15s, 60°C for 1 min. Reactions are performed in triplicate.

Primers (f & r) and FRET probes sets are designed using Primer Express Software (Perkin-Elmer). Probes are labeled at the 5'-end with the reporter dye 6-FAM and on the 3'-end with the quencher dye TAMRA (Biosource International, Camarillo, CA or Perkin-Elmer).

Example 31: Production Of Polypeptide of the Invention For High-Throughput Screening Assays

The following protocol produces a supernatant containing polypeptide of the present invention to be tested. This supernatant can then be used in the Screening Assays described in Examples 33-42.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel

pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2 x 10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degree C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of CaCl2 (anhyd); 0.00130 mg/L CuSO4-5H2O; 0.050 mg/L of Fe(NO3)3-9H2O; 0.417 mg/L of FeSO4-7H2O; 311.80 mg/L of Kcl; 28.64 mg/L of MgCl2; 48.84 mg/L of MgSO4; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO3; 62.50 mg/L of NaH2PO4-H20; 71.02 mg/L of Na2HPO4; .4320 mg/L of ZnSO4-7H2O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L

of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H20; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H20; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H20; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalainine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tryrosine-2Na-2H20; and 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B12; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust osmolarity to 327 mOsm) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 33-40.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supernatant.

Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 32: Construction of GAS Reporter Construct

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO: 8556)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is

encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

	JAKs				STATS	GAS(elements) or ISRE
Ligand	tyk2	Jak1	Jak2	Jak3		
IFN family						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g		+	+	-	1	GAS
(IRF1>Lys6>IFP)						
Il-10	+	?	?	-	1,3	
gp130 family						
IL-6 (Pleiotrohic)	+	+	+	?	1,3	GAS
(IRF1>Lys6>IFP)						
Il-11(Pleiotrohic)	?	+	?	?	1,3	
OnM(Pleiotrohic)	?	+	+	?	1,3	
LIF(Pleiotrohic)	?	+	+	?	1,3	
CNTF(Pleiotrohic)	-/+	+	+	?	1,3	
G-CSF(Pleiotrohic)	?	+	?	?	1,3	
IL-12(Pleiotrohic)	+	-	+	+	1,3	
g-C family						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP
>>Ly6)(IgH)						
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
gp140 family						
IL-3 (myeloid)	-	-	+	-	5	GAS
(IRF1>IFP>>Ly6)						
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS

<u>Growth hormone family</u>						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
<u>Receptor Tyrosine Kinases</u>						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	
CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 33-34, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAAT GATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:8557)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:8558)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':<u>CTCGAG</u>ATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATT TCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACT CCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTG ACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCC AGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAA<u>AAGCTT</u>:3' (SEQ ID NO:8559)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the

GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 33-34.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 35 and 36. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 33: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml genticin selected. Resistant colonies are expanded and then

tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1 x 10^7 cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptide of the present invention or polypeptide of the present invention induced polypeptides as produced by the protocol described in Example 31.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degree C until SEAP assays are performed according to Example 37. The plates containing the remaining treated

cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

Example 34: High-Throughput Screening Assay Identifying Myeloid Activity.

The following protocol is used to assess myeloid activity of polypeptide of the present invention by determining whether polypeptide of the present invention proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 32, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest 2x10e7 U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM Na2HPO4.7H2O, 1 mM MgCl2, and 675 uM CaCl2. Incubate at 37 degrees C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting $1x10^8$ cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium,

with a final density of $5x10^5$ cells/ml. Plate 200 ul cells per well in the 96-well plate (or $1x10^5$ cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 31. Incubate at 37 degee C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 37.

Example 35: High-Throughput Screening Assay Identifying Neuronal Activity.

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed by polypeptide of the present invention.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by polypeptide of the present invention can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO: 8560)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO: 8561)

Using the GAS:SEAP/Neo vector produced in Example 32, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified

product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 31. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as 5x105 cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to 1x105 cells/well). Add 50 ul supernatant produced by Example 31, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 37.

Example 36: High-Throughput Screening Assay for T-cell Activity.

NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of

agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 31. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:8562), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTC
CATCCTGCCATCTCAATTAG:3' (SEQ ID NO:8563)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:8558)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCATCTG
CCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCC
CTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTAT
TTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGG

AGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:8564)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 33. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 33. As a positive control, exogenous TNF alpha (0.1,1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 37: Assay for SEAP Activity.

As a reporter molecule for the assays described in Examples 33-36, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the

results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11

43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 38: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability.

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO_2 incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4 , 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO_2 incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10^6 cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4

solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to $1x10^6$ cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4 . The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a molecule induced by polypeptide of the present invention, which has resulted in an increase in the intracellular Ca++ concentration.

Example 40: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity.

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase

activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 31, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4, 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boeheringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4oC. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg2+ (5mM ATP/50mM MgCl2), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl2, 5 mM MnCl2, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavadin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 41: High-Throughput Screening Assay Identifying Phosphorylation Activity.

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 40, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as

described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 31 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

Example 42: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation.

This assay is based on the ability of human CD34+ to proliferate in the presence of

hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5 x 10^5 cells/ml. During this time, 100 μl of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10 μl of prepared cytokines, 50 μl of the supernatants prepared in Example 31 (supernatants at 1:2 dilution = 50 μl) and 20 μl of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100 μl. The plates are then placed in a 37°C/5% CO_2 incubator for five days.

Eighteen hours before the assay is harvested, 0.5 μCi/well of [3H] Thymidine is added in a 10 μl volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec

Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 μl Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell proliferation and/or to decrease the inhibition of cell proliferation in the presence of cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

Example 43: Assay for Extracellular Matrix Enhanced Cell Response (EMECR).

The objective of the Extracellular Matrix Enhanced Cell Response (EMECR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the

stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the $\alpha_5.\beta_1$ and $\alpha_4.\beta_1$ integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of 0.2 μg/ cm^2. Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Gene products of the invention (e.g., including, but not limited to, polynucleotides and polypeptides of the present invention, and supernatants produced in Example 31), are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5% CO_2, 7% O_2, and 88% N_2) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

If a particular polypeptide of the present invention is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene encoding said polypeptide may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or

agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

Example 44: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation.

The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNFa stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 µl culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 µg/ml hEGF, 5mg/ml insulin, 1µg/ml hFGF, 50mg/ml gentamycin, 50 µg/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours, culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2%

FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50μg/ml Amphotericin B, 0.4% FBS. Incubate at 37°C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed such that they always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFa is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or polypeptides of the present invention and incubate at 37°C/5% CO_2 until day 5.

Transfer 60μl from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4°C until Day 6 (for IL6 ELISA). To the remaining 100 μl in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10μl). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 ul/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 μl/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 μl/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker. Plates are washed with wash buffer and blotted on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 μl/well. Cover the plate and incubate 1 h at RT. Plates are again washed with wash buffer and blotted on paper towels. Add 100 μl/well of Enhancement Solution and shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay are tabulated and averaged.

A positive result in this assay suggests AoSMC cell proliferation and that the polypeptide of the present invention may be involved in dermal fibroblast proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of

polypeptides, polynucleotides, agonists and/or antagonists of the polynucleotide/polypeptide of the present invention which gives a positive result. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the present invention and polynucleotides of the present invention may be used in wound healing and dermal regeneration, as well as the promotion of vasculargenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides and polynucleotides of the invention may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides and polynucleotides of the invention may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 45: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells.

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 µl of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 µl volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 µl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10 µl of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 µg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 µl of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution, refered to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNNP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The plate is read on a plate reader

at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

Example 46: Alamar Blue Endothelial Cells Proliferation Assay.

This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from

oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

Example 47: Detection of Inhibition of a Mixed Lymphocyte Reaction.

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM®, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2 x 10^6 cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2 x 10^5 cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50 μl) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 μg/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final

concentration of 10 μg/ml. Cells are cultured for 7-8 days at 37°C in 5% CO_2, and 1 μC of [^{3}H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 48: Assays for Protease Activity.

The following assay may be used to assess protease activity of the colon or colon cancer related polypeptides of the invention.

Gelatin and casein zymography are performed essentially as described (Heusen et al., *Anal. Biochem.*, 102:196-202 (1980); Wilson et al., *Journal of Urology*, 149:653-658 (1993)). Samples are run on 10% polyacryamide/0.1% SDS gels containing 1% gelain orcasein, soaked in 2.5% triton at room temperature for 1 hour, and in 0.1M glycine, pH 8.3 at 37°C 5 to 16 hours. After staining in amido black areas of proteolysis apear as clear areas agains the blue-black background. Trypsin (Sigma T8642) is used as a positive control.

Protease activity is also determined by monitoring the cleavage of n-a-benzoyl-L-arginine ethyl ester (BAEE) (Sigma B-4500. Reactions are set up in (25mMNaPO_4,1mM EDTA, and 1mM BAEE), pH 7.5. Samples are added and the change in adsorbance at 260nm is monitored on the Beckman DU-6 spectrophotometer in the time-drive mode. Trypsin is used as a positive control

Additional assays based upon the release of acid-soluble peptides from casein or hemoglobin measured as adsorbance at 280 nm or colorimetrically using the Folin method are performed as described in Bergmeyer, et al., *Methods of Enzymatic Analysis*, 5 (1984). Other assays involve the solubilization of chromogenic substrates (Ward, *Applied Science*, 251-317 (1983).

Example 49: Identifying Serine Protease Substrate Specificity.

Methods known in the art or described herein may be used to determine the substrate specificity of the polypeptides of the present invention having serine protease activity. A preferred method of determining substrate specificity is by the use of positional scanning synthetic combinatorial libraries as described in GB 2 324 529 (incorporated herein in its entirety).

Example 50: Ligand Binding Assays.

The following assay may be used to assess ligand binding activity of the colon or colon cancer related polypeptides of the invention.

Ligand binding assays provide a direct method for ascertaining receptor pharmacology and are adaptable to a high throughput format. The purified ligand for a colon or colon cancer related polypeptide is radiolabeled to high specific activity (50-2000 Ci/mmol) for binding studies. A determination is then made that the process of radiolabeling does not diminish the activity of the ligand towards its colon or colon cancer related polypeptide. Assay conditions for buffers, ions, pH and other modulators such as nucleotides are optimized to establish a workable signal to noise ratio for both membrane and whole cell colon or colon cancer related polypeptide sources. For these assays, specific colon or colon cancer related polypeptide binding is defined as total associated radioactivity minus the radioactivity measured in the presence of an excess of unlabeled competing ligand. Where possible, more than one competing ligand is used to define residual nonspecific binding.

Example 51: Functional Assay in Xenopus Oocytes.

Capped RNA transcripts from linearized plasmid templates encoding the colon or colon cancer related antigen cDNAs of the invention are synthesized in vitro with RNA polymerases in accordance with standard procedures. In vitro transcripts are suspended in water at a final concentration of 0.2 mg/mi. Ovarian lobes are removed from adult female toads, Stage V defolliculated oocytes are obtained, and RNA transcripts (10 ng/oocytc) are

injected in a 50 nl bolus using a microinjection apparatus. Two electrode voltage clamps are used to measure the currents from individual *Xenopus oocytes* in response to colon cancer antigen or colon cancer antigen agonist exposure. Recordings are made in Ca2+ free Barth's medium at room temperature. The Xenopus system can be used to screen known ligands and tissue/cell extracts for activating ligands.

Example 52: Microphysiometric Assays.

Activation of a wide variety of secondary messenger systems results in extrusion of small amounts of acid from a cell. The acid formed is largely as a result of the increased metabolic activity required to fuel the intracellular signaling process. The pH changes in the media surrounding the cell are very small but are detectable by the CYTOSENSOR microphysiometer (Molecular Devices Ltd., Menlo Park, Calif.). The CYTOSENSOR is thus capable of detecting the activation of a colon cancer antigen which is coupled to an energy utilizing intracellular signaling pathway.

Example 53: Extract/Cell Supernatant Screening.

A large number of mammalian receptors exist for which there remains, as yet, no cognate activating ligand (agonist). Thus, active ligands for these receptors may not be included within the ligands banks as identified to date. Accordingly, the colon cancer antigen of the invention can also be functionally screened (using calcium, cAMP, microphysiometer, oocyte electrophysiology, etc., functional screens) against tissue extracts to identify its natural ligands. Extracts that produce positive functional responses can be sequentially subfractionated until an activating ligand is isolated identified.

Example 54: Calcium and cAMP Functional Assays.

Seven transmembrane receptors which are expressed in HEK 293 cells have been shown to be coupled functionally to activation of PLC and calcium mobilization and/or cAMP stimulation or inhibition. Basal calcium levels in the HEK 293 cells in receptor-transfected or vector control cells were observed to be in the normal, 100 nM to 200 nM,

range. HEK 293 cells expressing recombinant receptors are loaded with fura 2 and in a single day >150 selected ligands or tissue/cell extracts are evaluated for agonist induced calcium mobilization. Similarly, HEK 293 cells expressing recombinant receptors are evaluated for the stimulation or inhibition of cAMP production using standard cAMP quantitation assays. Agonists presenting a calcium transient or cAMP fluctuation are tested in vector control cells to determine if the response is unique to the transfected cells expressing receptor.

Example 55: ATP-binding assay.

The following assay may be used to assess ATP-binding activity of the colon or colon cancer related polypeptides of the invention.

ATP-binding activity of the colon or colon cancer related polypeptides of the invention may be detected using the ATP-binding assay described in U.S. Patent 5, 858, 719, which is herein incorporated by reference in its entirety. Briefly, ATP-binding to colon or colon cancer related polypeptides of the invention is measured via photoaffinity labeling with 8-azido-ATP in a competition assay. Reaction mixtures containing 1 mg/ml of the ABC transport protein of the present invention are incubated with varying concentrations of ATP, or the non-hydrolyzable ATP analog adenyl-5'-imidodiphosphate for 10 minutes at 4°C. A mixture of 8-azido-ATP (Sigma Chem. Corp., St. Louis, MO.) plus 8-azido-ATP (-^{32}P-ATP) (5 mCi/μmol, ICN, Irvine CA.) is added to a final concentration of 100 μM and 0.5 ml aliquots are placed in the wells of a porcelain spot plate on ice. The plate is irradiated using a short wave 254 nm UV lamp at a distance of 2.5 cm from the plate for two one-minute intervals with a one-minute cooling interval in between. The reaction is stopped by addition of dithiothreitol to a final concentration of 2mM. The incubations are subjected to SDS-PAGE electrophoresis, dried, and autoradiographed. Protein bands corresponding to the particular colon or colon cancer related polypeptides of the invention are excised, and the radioactivity quantified. A decrease in radioactivity with increasing ATP or adenly-5'-imidodiphosphate provides a measure of ATP affinity to the colon or colon cancer related polypeptides.

Example 56: Small Molecule Screening.

This invention is particularly useful for screening therapeutic compounds by using the colon or colon cancer related polypeptides of the invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a colon or colon cancer related polypeptide of the invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the colon or colon cancer related e polypeptides of the invention. These methods comprise contacting such an agent with a colon or colon cancer related polypeptide of the invention or a fragment thereof and assaying for the presence of a complex between the agent and the colon or colon cancer related polypeptides or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the colon or colon cancer related polypeptides of the invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the colon or colon cancer related polypeptides of the invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is herein incorporated by reference in its entirety. Briefly stated, large numbers of different small molecule test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The test compounds are reacted with colon or colon cancer related polypeptides of the invention and washed. Bound colon or colon cancer related polypeptides are then detected by methods well known in the art. Purified colon or colon cancer related polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding colon or colon cancer related polypeptides of the invention specifically compete with a test compound for binding to the colon or colon cancer related polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a colon or colon cancer related polypeptides.

Example 57: Phosphorylation Assay.

In order to assay for phosphorylation activity of the colon or colon cancer related polypeptides of the invention, a phosphorylation assay as described in U.S. Patent 5,958,405 (which is herein incorporated by reference) is utilized. Briefly, phosphorylation activity may be measured by phosphorylation of a protein substrate using gamma-labeled ^{32}P-ATP and quantitation of the incorporated radioactivity using a gamma radioisotope counter. The colon or colon cancer related polypeptides of the invention are incubated with the protein substrate, ^{32}P-ATP, and a kinase buffer. The ^{32}P incorporated into the substrate is then separated from free ^{32}P-ATP by electrophoresis, and the incorporated ^{32}P is counted and compared to a negative control. Radioactivity counts above the negative control are indicative of phosphorylation activity of the colon or colon cancer related polypeptides of the invention.

Example 58: Detection of Phosphorylation Activity (Activation) of Colon or Colon Cancer Related Polypeptides of the Invention in the Presence of Colon or Colon Cancer Related Polypeptides Ligands.

Methods known in the art or described herein may be used to determine the phosphorylation activity of the colon or colon cancer related polypeptides of the invention. A preferred method of determining phosphorylation activity is by the use of the tyrosine phosphorylation assay as described in US 5,817,471 (incorporated herein by reference).

Example 59: Identification Of Signal Transduction Proteins That Interact With Colon or Colon Cancer Related Polypeptides Of The Present Invention.

The inventive purified colon or colon cancer related polypeptides of the invention are research tools for the identification, characterization and purification of additional signal transduction pathway proteins or receptor proteins. Briefly, labeled receptor PTK polypeptide is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, receptor PTK polypeptide is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as carcinoma tissues, is passed over the column, and molecules with appropriate affinity bind to the receptor PTK polypeptides, or specific phosphotyrosine-recognition domains thereof. The receptor PTK polypeptide interacting protein-complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

Example 60: IL-6 Bioassay.

To test the proliferative effects of the colon or colon cancer related polypeptides of the invention, the IL-6 Bioassay as described by Marz *et al.* is utilized (*Proc. Natl. Acad. Sci., U.S.A., 95*:3251-56 (1998), which is herein incorporated by reference). Briefly, IL-6 dependent B9 murine cells are washed three times in IL-6 free medium and plated at a concentration of 5,000 cells per well in 50 μl, and 50 μl of the IL-6-like polypeptide is added. After 68 hrs. at 37°C, the number of viable cells is measured by adding the tetrazolium salt thiazolyl blue (MTT) and incubating for a further 4 hrs. at 37°C. B9 cells are lysed by SDS and optical density is measured at 570 nm. Controls containing IL-6 (positive) and no cytokine (negative) are utilized. Enhanced proliferation in the test sample(s) relative to the negative control is indicative of proliferative effects mediated by colon or colon cancer related polypeptides of the invention.

Example 61: Support of Chicken Embryo Neuron Survival.

To test whether sympathetic neuronal cell viability is supported by the colon or colon cancer related polypeptides of the invention, the chicken embryo neuronal survival assay of Senaldi *et al* is utilized (*Proc. Natl. Acad. Sci., U.S.A., 96*:11458-63 (1998), which is herein

incorporated by reference). Briefly, motor and sympathetic neurons are isolated from chicken embryos, resuspended in L15 medium (with 10% FCS, glucose, sodium selenite, progesterone, conalbumin, putrescine, and insulin; Life Technologies, Rockville, MD.) and Dulbecco's modified Eagles medium [with 10% FCS, glutamine, penicillin, and 25 mM Hepes buffer (pH 7.2); Life Technologies, Rockville, MD.], respectively, and incubated at 37°C in 5% CO_2 in the presence of different concentrations of the inventive purified IL-6-like polypeptide, as well as a negative control lacking any cytokine. After 3 days, neuron survival is determined by evaluation of cellular morphology, and through the use of the colorimetric assay of Mosmann (Mossman, T., *J. Immunol. Methods, 65*:55-63 (1983)). Enhanced neuronal cell viability as compared to the controls lacking cytokine is indicative of the ability of the inventive purified IL-6-like polypeptide(s) to enhance the survival of neuronal cells.

Example 62: Assay for Phosphatase Activity.

The following assay may be used to assess serine/threonine phosphatase (PTPase) activity of the colon or colon cancer related polypeptides of the invention.

In order to assay for serine/threonine phosphatase (PTPase) activity, assays can be utilized which are widely known to those skilled in the art. For example, the serine/threonine phosphatase (PSPase) activity is measured using a PSPase assay kit from New England Biolabs, Inc. Myelin basic protein (MyBP), a substrate for PSPase, is phosphorylated on serine and threonine residues with cAMP-dependent Protein Kinase in the presence of [γ-^{32}P]ATP. Protein serine/threonine phosphatase activity is then determined by measuring the release of inorganic phosphate from 32P-labeled MyBP.

Example 63: Interaction of Serine/Threonine Phosphatases with other Proteins.

The colon or colon cancer related polypeptides of the invention with serine/threonine phosphatase acitivity as determined in Example 62 are research tools for the identification, characterization and purification of additional interacting proteins or receptor proteins, or other signal transduction pathway proteins. Briefly, a labeled colon or colon cancer related polypeptides of the invention is useful as a reagent for the purification of molecules with

which it interacts. In one embodiment of affinity purification, colon or colon cancer related polypeptides of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as neural or liver cells, is passed over the column, and molecules with appropriate affinity bind to the colon or colon cancer related polypeptides of the invention. The colon or colon cancer related polypeptides of the invention-complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

Example 64: Assaying for Heparanase Activity.

In order to assay for heparanase activity of the colon or colon cancer related polypeptides of the invention, the heparanase assay described by Vlodavsky et al is utilized (Vlodavsky, I., et al., Nat. Med., 5:793-802 (1999)). Briefly, cell lysates, conditioned media or intact cells (1 x 10^6 cells per 35-mm dish) are incubated for 18 hrs at 37°C, pH 6.2-6.6, with ^{35}S-labeled ECM or soluble ECM derived peak I proteoglycans. The incubation medium is centrifuged and the supernatant is analyzed by gel filtration on a Sepharose CL-6B column (0.9 x 30 cm). Fractions are eluted with PBS and their radioactivity is measured. Degradation fragments of heparan sulfate side chains are eluted from Sepharose 6B at $0.5 < K_{av} < 0.8$ (peak II). Each experiment is done at least three times. Degradation fragments corresponding to "peak II," as described by Vlodavsky et al., is indicative of the activity of the colon or colon cancer related polypeptides of the invention in cleaving heparan sulfate.

Example 65: Immobilization of biomolecules.

This method provides a method for the stabilization of colon or colon cancer related polypeptides of the invention in non-host cell lipid bilayer constucts (see, e.g., Bieri et al., Nature Biotech 17:1105-1108 (1999), hereby incorporated by reference in its entirety herein) which can be adapted for the study of colon or colon cancer related polypeptides of the invention in the various functional assays described above. Briefly, carbohydrate-specific chemistry for biotinylation is used to confine a biotin tag to the extracellular domain of the

colon or colon cancer related polypeptides of the invention, thus allowing uniform orientation upon immobilization. A 50uM solution of colon or colon cancer related polypeptides of the invention in washed membranes is incubated with 20 mM NaIO4 and 1.5 mg/ml (4mM) BACH or 2 mg/ml (7.5mM) biotin-hydrazide for 1 hr at room temperature (reaction volume, 150ul). Then the sample is dialyzed (Pierce Slidealizer Cassett, 10 kDa cutoff; Pierce Chemical Co., Rockford IL) at 4C first for 5 h, exchanging the buffer after each hour, and finally for 12 h against 500 ml buffer R (0.15 M NaCl, 1 mM MgCl2, 10 mM sodium phosphate, pH7). Just before addition into a cuvette, the sample is diluted 1:5 in buffer ROG50 (Buffer R supplemented with 50 mM octylglucoside).

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties. Moreover, the hard copy of and the corresponding computer readable form of the Sequence Listing of U.S. Patent Application Serial No. 60/157,137 and 60/163,280 are also incorporated herein by reference in its entirety.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

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NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209061
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
20 May 1997	209062

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only	For International Bureau use only
☐ This sheet was received with the international application	☐ This sheet was received by the International Bureau on:
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ATCC Deposit No. 209062
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

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ATCC Deposit No. 209062
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
20 May 1997	209063

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).
Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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ATCC Deposit No. 209063
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

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ATCC Deposit No. 209063
Page 3

DENMARK

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SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
20 May 1997	209064

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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ATCC Deposit No. 209064
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

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ATCC Deposit No. 209064
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
20 May 1997	209065

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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ATCC Deposit No. 209065
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

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ATCC Deposit No. 209065
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
20 May 1997	209066

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

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Authorized officer	Authorized officer

ATCC Deposit No. 209066
Page 2

CANADA

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FINLAND

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UNITED KINGDOM

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ATCC Deposit No. 209066
Page 3

DENMARK

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
20 May 1997	209067

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).
Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only	For International Bureau use only
☐ This sheet was received with the international application	☐ This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

ATCC Deposit No. 209067
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

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ATCC Deposit No. 209067
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
20 May 1997	209068

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).
Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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Authorized officer	Authorized officer

ATCC Deposit No. 209068
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

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ATCC Deposit No. 209068
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13 *bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
20 May 1997	209069

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).
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E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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ATCC Deposit No. 209069
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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ATCC Deposit No. 209069
Page 3

DENMARK

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SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
12 January 1998	209579

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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ATCC Deposit No. 209579
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

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ATCC Deposit No. 209579
Page 3

DENMARK

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SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
12 January 1998	209578

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

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ATCC Deposit No. 209578
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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FINLAND

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UNITED KINGDOM

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ATCC Deposit No. 209578
Page 3

DENMARK

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
16 July 1998	203067

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

Continued on the Attached Pages 2 & 3

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ATCC Deposit No. 203067
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203067
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
16 July 1998	203068

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only	For International Bureau use only
☐ This sheet was received with the international application	☐ This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

ATCC Deposit No. 203068
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203068
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet [X]

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
01 February 1999	203609

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet [ ]

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).
Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer	Authorized officer

ATCC Deposit No. 203609
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203609
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311 , line N/A .

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
01 February 1999	203610

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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ATCC Deposit No. 203610
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203610
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
17 November 1998	203485

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only	For International Bureau use only
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ATCC Deposit No. 203485
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203485
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
18 June 1999	PTA-252

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only	For International Bureau use only
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Authorized officer	Authorized officer

ATCC Deposit No. PTA-252
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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ATCC Deposit No. PTA-252
Page 3

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
18 June 1999	PTA-253

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

Continued on the Attached Pages 2 & 3

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only	For International Bureau use only
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ATCC Deposit No. PTA-253
Page 2

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

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ATCC Deposit No. PTA-253
Page 3

DENMARK

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SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 311, line N/A.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
28 October 1999	PTA-881

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).
Continued on the Attached Pages 2 & 3

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ATCC Deposit No. PTA-881
Page 2

CANADA

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ATCC Deposit No. PTA-881
Page 3

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Applicant's or agent's file reference number	PA005PCT	International application No.	UNASSIGNED

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Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
28 October 1999	PTA-882

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

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Continued on the Attached Pages 2 & 3

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ATCC Deposit No. PTA-882
Page 2

CANADA

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ATCC Deposit No. PTA-882
Page 3

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What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X which is hybridizable to SEQ ID NO:X;

(b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y which is hybridizable to SEQ ID NO:X;

(d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y which is hybridizable to SEQ ID NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

(i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X, which is hybridizable to SEQ ID NO:X.

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y;
(b) a polypeptide fragment of SEQ ID NO:Y, having biological activity;
(c) a polypeptide domain of SEQ ID NO:Y;
(d) a polypeptide epitope of SEQ ID NO:Y;
(e) a full length protein of SEQ ID NO:Y;
(f) a variant of SEQ ID NO:Y;
(g) an allelic variant of SEQ ID NO:Y; or
(h) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:

(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

(a) expressing SEQ ID NO:X in a cell;

(b) isolating the supernatant;

(c) detecting an activity in a biological assay; and

(d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

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ttttggccat tctaatggat atgtagcggt atctcattat tttaatttgc attttcttga 1380
tgacatatga tgtcgagcat ctcttcatat gcgtatccat ctgtatacct nctttggtga 1440
ggtgtctgtt aaggtctntg atncatttta atgcttcttt gttaggggta gatacatgta 1500
aaggatatgt cttcttggag aattgactcc tttatcctta tataataatc ctctttgttc 1560
cttgtaactt gcattgctgt gcaatttgct ctttctgaaa ttagcacaat tgacccttga 1620
atgacatgga ggttaggggc acaaatgaaa atctgtgtat aactttttat tcatctataa 1680
cttaactttt aaacccattt aacctccccc caaaattcag gaataataac acacccgacc 1740
acaccgctta caaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1800
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 1843

<210> 5
<211> 471
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (161)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (428)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (471)
<223> n equals a,t,g, or c

<400> 5
ggaagaagcc cagaggttgt gcccaggggc agaaatcatt gcctagtgtt caccggctga 60
ctctcaactg accattccca tgtggacagg ccttaatact gtgagaggat ccttgctctg 120
ctggcagttt cccactccta tgcactttca caggaactag naaaactatt cttaaaccaa 180
aaataccatc cgtgttgacc catgttgcag agcccttact taaatccttc actggtgtat 240
gaatactttg tcataatgct gctttgctgg gtagtgagct cttatttttc actgggggtc 300
agctataact aaaaactcaa gtgacatatt tcagttacca aagtggccag gaacttttttg 360
cttttatgaa aatagattca tattgtattt cccagtgtgt cttytatgtc tttgaatgtt 420
ttagaganaa gtctatgcct gtctaaaaat gaatccagtg ttgcctttct n 471

<210> 6
<211> 905

<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (836)
<223> n equals a,t,g, or c

<400> 6
gttctagatc gcgagcggcc gcccttttt tttttgatt tatatgaact tgcaaatcat 60
atatattaac cttttgttat gtggagattt tggacaggag gattgcttga ggccaggaat 120
tcaagaccag cctgggaaac aaagtgagac cctgtcttta caaaaaataa aaacaaaaat 180
ttaaaactgt ataatctgca ctttatgcta aactagctgt gctcttaaac tcaattttt 240
cagctctaat aaagggctta atttgataga attattctac gattaaattt tgaagactgt 300
tttcactctc ctctgccgcc catagcaaga ctgcttccat agatttctca gaaccgtagc 360
cagttctggc tatttggtca agtctgggat ccctcttacc tgctattctg cagctgcttt 420
ctctgtctta catttttgg gccacgtcta atcttaaaga gtaaactcta cccttggttt 480
gcatagtgtg catgacaaaa ataacaagaa taatggtaat gatgaaaatg ataagagcaa 540
aatttgtgga gtgctttcca cattccaggt aatgtgtaac atacaattta attcttacag 600
cagtcttatg gagtgaaaat actattatga attcccgttt tacagatgaa agaatggagg 660
cacagaaaag ttacttgtct aagtaacagt ctatccttaa agtccacagt cttaaccact 720
tggatttttc atagtgaggg aaaatatccc agaaagttgc agtttcaatt aatcactgaa 780
ttgtagggta atttaactat accagtgaag tgcctactga gcagaaatat ttgggncaac 840
atgaagccca ctggactggg agcttttgtt ttagcataat gaacctgttt ccagcaagat 900
tttga 905

<210> 7
<211> 412
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (108)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (372)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (377)
<223> n equals a,t,g, or c

<400> 7
aattcggcac gaggaaactt gctattccac ccacaccaag ttaaaaagga aaaaaaaaag 60
actttcgcac aattgtttcc taactgataa cattgtacat tcttaggnga ttagtaattg 120
tgtgaaattt actcatactg tttctaagtt tttcagcata gtcattgcac ttcagcaggg 180
aatctgagta tactttacag acagagtgaa cttaaaagtt taatgtcaag agattatggc 240

ttaaataaat tagtgtgtcc tatagggga aaaaaaccaa gaaaccacct tttaaaaaga 300
atgatatgcc atataccctt ggattttcat tttgcattat attgacgtgt ttttttgaag 360
ggaaaaaaag tnataanaat ctggatagtc taagactcca ctattttaaa ag 412

<210> 8
<211> 752
<212> DNA
<213> Homo sapiens

<400> 8
actgaacagt ggttaatcct gactctgttt ttgactgaca gttaacagtt acatgaacca 60
ttcatattac agctcttact taaatttgac caagccagga tatatctgtt aggccacatt 120
catttaggga tcatgttttc caaagcaggt ttgggcaaaa ttaatccaca ggactgaaag 180
gtatacatct gtgagttttg ttctcacttc cacctctaat ttgaagaaca ctttaattga 240
cacagaatac atttcacata tttaacctct acaataagtt ctgacacatt ttccatgaaa 300
caaaccatcg ctatattcaa gataatgaac ctatctatca tactcccaaa ttccttctkg 360
catctttgta atttctcact cttccttctc cctctccccg tcccatccca accactgatc 420
tgctcaggca actaccaatc ttctttctgt cactatagat taatttgcat ttttaaagaa 480
atttacatac atggaaccat acatcatcta tgctttgtag tatgactcct gtcactcagt 540
acaattattt tgagattcat ttatgttawt gtatgtatca atagttcatc ccttttattg 600
gtaagtaaca ttttttgta taggtatacc atgatttgtt gatgaacaaa tttacctgtt 660
gatgaacatt tacgttgtta ccaagatttt tgctattgaa aataaagttt ttatgaatat 720
ttatatatat aaaaaaaaaa aaaaaaactc ga 752

<210> 9
<211> 642
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (613)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (622)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (635)
<223> n equals a,t,g, or c

<400> 9
ggcagaggtg ctactggaag caatacgaaa aggtattcag ctacgcaaag tagaagagca 60
gcgtgaacag gaagctaagc atgaacgcat tgaaaacgat gttgccacca tcctgtctcg 120
ccgtattgct gttgaatata gtgattcgga agatgattca gaatttgatg aagtagattg 180
gttggagtaa gaaaaatgca ttgataaata ttacaaaact gaatgcaaat gtcctttgtg 240
gtgcttgttc cttgaaaatg tttggtcatt ctagtgtttt gctttctttt ccttataata 300
aatgaccctt ttcctccata acttttgatt tctaaggaaa atattagcat acatttcaaa 360

ctaaatgttt tacagtggct tatctttttt ttccccctga aaagactaat ttggtcaaat 420
aaaccactaa gtattaagca tgggacagct gttgttagga gtagccagat tcagtttttt 480
ggatatatct taattgtgta ctttgtggaa ttttaaattt aaaggaaagg caactggaaa 540
ttggaaatcy tgaggggcag ctgtatctac taatgaggcc ttattccctt tcccggatgt 600
tttaaaggag ggnacactgc cntggattat acggntacac cc 642

<210> 10
<211> 211
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (210)
<223> n equals a,t,g, or c

<400> 10
tctttttctc tcccactttt tcatattcct ctttttcatt tttgcctttc cgtttctgtc 60
tatgatgtag gcttctgagg agaaccmaga agcttggctt tagtggtaga atgacagrac 120
ttagggatcc cttgcaggct agaacaaagt tctgaccctt agaccaaatc tttatgttaa 180
gaagttttcc agaattcaaa aaaaaaaaan t 211

<210> 11
<211> 532
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (515)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (517)
<223> n equals a,t,g, or c

<400> 11
taagagatca aagcttataa ttttcttttt taatttttga aggagggatc aactccagtt 60
tccaatgtct atgtgtctat gtgtgtatgt gccatacata tgtattcaca tgaagaccgg 120
catggccaag ttctgctgga ggagcactca agtgtgacga gcagggccac tggaccctgc 180
agggctgtgg tgtatatagt gcagctttgg aggtggaact ctattttcac acttttctat 240
ggagccttcc gagtcccagg ttttcacttg aggctgtctg tctggatggc ggttttcaga 300
cctccattaa catccctacc cagcattctg tacttcgggg gccttctctc ttgttataaa 360
actttttacc aagtgaaaca tcgataccac ctttgtttcc attctcactg gtgtaaatac 420
tgagtactaa ctgagaattt tgactttgca ttctgtcgga atacttgtgt tcaataaaaa 480
ttgaaagaaa aaagctaaaa aaaaaaaaaa aaaancncga gggggggccc gg 532

<210> 12
<211> 1120
<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (711)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (946)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (987)
<223> n equals a,t,g, or c

<400> 12
cataaacatt gatgttgggt caatcatgtt ctcaatgtat ttaaccatgt gtttttaaat 60
tttttaattt agttatcaaa ttgagaatct gatggtatgg cattaatcac cttgaggaag 120
aacctttatc gtttatctga ttttcagatg catagagctc tggctgcttt aaaaaataaa 180
cctctaaatc atgttcacaa ggtagtcaag gagcgtctgt gcccttggtt gtgttcacga 240
caacctgagc ctttcggggt cagattccat catgcccatt gtaaaaagtt tcattcgaaa 300
aatggaaatg accttcatcc actcggtgga ccagtgttct ctcaagtatc tgactgcgac 360
aggcttgaac aaaatgttaa aaatgaggag agtcagatgt tttacaggag actgagcaac 420
ttgacttcat cagaagaagt gctaagtttt ataagcacga tggaaaccct gcctgacact 480
atggcagcag gagctttaca acggatttgt gaagtggaaa aaaaggatgg tgatcaaggg 540
ctgccaaaag raatactgga gaatagcatc tttcaagctt tatgctttca gtttgaaaag 600
gagccctcac agctgtcaaa cactagttta gtgactgctt tkcaagctct gattctgttg 660
catgtggatc ctcaaagtag cctgttgctg aacctggtgg cagaatgcaa naatcgtctc 720
agaaaaggtg gcatggaagt tcgcaatctt tgtattcttg gggaaagtct gattacactg 780
cacagttcag gttgtgtgac actagaactc attataaatc aacttcaagg tgaaaaattg 840
gaaacattta ccccggagga tattgtggcc ctttatagaa tcttgcaggc atgtactgaa 900
aaagtggatg aacaccaaac atttttaaat aagataaaca actttnccct atcaatagtt 960
tccaacctga gtcctaaatt gattagncaa atgctcactg ccctggtggt tcttgatcaa 1020
agtcaagcat ttcctctgat tataaaattg ggcaaaatat gtcgtgaggc atgtcccaca 1080
tttcacttaa cgaggagctt aggagagtct tttgaggcgt 1120

<210> 13
<211> 600
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (50)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (571)

<223> n equals a,t,g, or c

<400> 13
ctagatcgtc agggaggaag ggtcagttgg gtgcctgttt ttctgttttn agtcctttaa 60
aatgagtaga agcaacctgt taccctggaa agagcactgg acatagacct agtgctgcgt 120
gatgttgagc acgtttcttc ttccctttga gtcccagttt cccttttggt tacaggggga 180
tagtagcccc cagggatcat gtgaaagtga gaaagccctt ttcacactgt ggagcggtgc 240
agatgtggga aacctcaaag atggttgccc attttaaatc ctttcatctc tcatctctct 300
ttcttctctc ccttctgccc tgacgtagcc atggttgggt gggtgaggcc agaagaaact 360
gcctccgmaa gaggtagcag ccgctcaggt ggctctgctg gcatcggagc ccacagaagt 420
gaggagtggc cgatggamct gccctccaaa tgtgcctgac tctgggtctt gctgtcactg 480
ggatttcctg ggcatggcag acagaaagaa agatagtttg accaagtcgt aggaagcttg 540
attccagcgg gtaaaaaagg gggcagggaa ntcgtccctt ttattttttg ccttcaggag 600

<210> 14
<211> 807
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (773)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (786)
<223> n equals a,t,g, or c

<400> 14
caattaaggg tgtacaaatt ataataatgc atctctatct tcatactttg aatggcaaac 60
gctatttatg cataaatatt ttcattttaa gtaatatatg aagtgtaaat actcgatata 120
taagtataga ttttaaagat atgggacttt attttcacat aagtcaatag atgtttctct 180
agaacaaaat atttagtaaa gctttataaa ttatattaaa aggaagcggg gaacatgtat 240
tttttaacat agaacagaag tgacttcatt ctttttagac atcagaaatg ttaaagttga 300
ttcccaatat ttgttgtact tttttgtagc aaatgttaaa aatcacgagt taccatgtat 360
agaatgtgga ctgtcatgtt gatatcattg tacagtgata agccattttw atctgtatac 420
atttcaccaa tttattaaca ggttgaatat ttgtttcttt ttagaacatt ttatttatac 480
tgtgaagact ttgttatacc ttatttgcta caacatagat catatcattg ctactttgac 540
ttagcatttg catcataaac ataattatga tgtttttttc atgctccttc caggggctca 600
gtcacttgaa gaaactgttg ctaaccaagc tcttgactct gtttccctta atgatacaag 660
tctctgtacc agcgctttat gttaattacc aaaactctcc tgcatcagag catgatatct 720
ataataggag atactgsaat aaaatgrttw ggctgtaaaa atttggaggc acnaattttc 780
caattncaat ggcaaattgg catggtg 807

<210> 15
<211> 416
<212> DNA
<213> Homo sapiens

<220>

<221> misc feature
<222> (1)
<223> n equals a,t,g, or c

<400> 15
ngttttggga ttattataag ttcttgtgtc ttaaggccat ctgcttttat atccagtgat 60
gtgggatttt aatcagccat taattaggta agcattcact ttgaggacaa tattctgttt 120
tatcttgggt agcatggaca gtttgtcaca gaaataagtt ccctattcaa acttggaatt 180
agctgattca gagtaacata ttaataatat aaaaatggcc ataccctttt atggcgtaac 240
attatttcta ggtattgttt ctaaggaaat aattttaaat attgggaaaa aatattttta 300
caatttacag tctgtctgac atttggtaaa tagctaattg tgatatattc atattaggag 360
atagggtgca gccactaaaa tgattttgaa gtattgtcca ttagtaatgg taattt 416

<210> 16
<211> 752
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (40)
<223> n equals a,t,g, or c

<400> 16
ggcctgggct ccttccgaat ggtggcgcct ctgagccagn tttcgaggag gagtcggagg 60
aggagcctga atgtttggag atagacttca agtcccggac cttatccgtg cgccgcttcg 120
gtttgcaggt gacctttgcg tgcgggcgcc ccttctgatt gaccctgatg agctgtagct 180
ctgatggccc ctccttcggg aatgattagg gtgacggctg kccggggctc gttcgagtgg 240
cgcccggccg gtggtgaccc gaacaggaga gcgggacggc gaccattctc tcgggagggs 300
cccatytgga gaaagtcctc tcgcttggtc aaactaggag ggcgatagca ccggccttac 360
tgcgacgatg acaaagtaca acacaccgtc tggcgcgaag gagatgctcg agaacccttt 420
gctgttgtta tttttcgcgt gtcctccgaa accaagggaa atgcggctct gtgggttctg 480
ttaacgtcag catttaataa gtgaactcta aatgcattgc cccttatggg tgcgctggcc 540
tcctgagttg actcagctct tgcaacgtag ctagttgata accctcgaaa tatagcgaat 600
tgagatgtgc tatattgtaa aatacgggac ttagtacgaa aaaactgatg taaaaattat 660
ctcaatactt tttaatactg attacatgtt ggaatataat gttttgcata tattgggtca 720
aataaaaatg ttattaattt caaaaaaaaa aa 752

<210> 17
<211> 481
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (442)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (447)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (448)
<223> n equals a,t,g, or c

<400> 17
ggcacgagtt tcaaaccaac actgaaattc tgtggcatca catatattgg gccttgatgt 60
catgacagak caaaatcatt tgatatccct ttctccattc taggtttttc tttttttcag 120
taactgattt accttgatca cttttcaact tccatattct tcatatagta aaaggcaaag 180
tgttgaagat actacggtgt ggtagtagtt gaaaattatt gccgtcatta tttacatact 240
taagacatat tagcaagttg atccaaaatg ggaggcctta tagatgtgct tgggggaaaa 300
tgaaggggag aaagtagcca tacaggagtt caaagaattc catgcccttc agattagccc 360
attaccagaa acatcatgaa agtattttaa aaactaatta tttactacag tgtatttcac 420
ttgtcttgtg tgtctgaaca cnagganngc taaattagca agttttttaa ggaggtattt 480
t 481

<210> 18
<211> 912
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (875)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (881)
<223> n equals a,t,g, or c

<400> 18
aattcggcac aggatcagac ttcctttcaa ctgtcctccc ctccaagcag accacctgtc 60
cccttctatc ccagctcaga gcagctgacc caactcagaa tctctttcct acaggatgaa 120
gtgccttttg aatgttattt taagccgaga gttaattttt ctacacaaca tatttccaga 180
catcttttag tcttttattg tcttagatac tataagaaga tgaacatgac aattttctag 240
aacctggtag cgtgtgtgtg tgtggcgggg ggtgctgagg gaggggagtg agtcacagga 300
gcctgtcccc caacaggtgt gactgctctg acaacctgtg gcatgctgca gggtcaggct 360
cctgatagga ggatttcatg actatgtcat tgtctccact catttttgac ccagtttgga 420
atgtatctgc aattgtgtgg ctcaacactt taggaaacaa tagattattt tatattatta 480
tttctgatgg tgacaagttt gtcttgaggt cacattttct ccttgaaaag tgacatcctg 540
tcacttctgc tctcacacta ctgccataca tttgtgtttt ttgttgttat tgtttgggta 600
gagcagttac aagaaaccct aaaacccttg gatataaaag aaatctgttt attgattttt 660
aaatctttcc tttccaaaag ctgggataca catgggagct gtttggggaa ttttccttgc 720
tgctaccgcg ctgccaccaa atgggaattg accaggcggg ctgtttacac tgtttctttg 780
gccactgtgg ccyatggctc aggaatatgg ctcactggct aaggcttacc aaactcgggg 840
acagggggtc agggaaacag gaggggtgtt ccccntcccc nttggcaggc cttcccaccc 900
acctggttaa cc 912

<210> 19
<211> 507
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (489)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (492)
<223> n equals a,t,g, or c

<400> 19
ggatacatag gaagttgacc tcggggtatc atggagagtg tccctcctag tggctggagg 60
tagggacagt tggttgtggg gctggagaga ggttgtgggg aggaagcgag gatgcgtgcc 120
tgccactagg atctgcatcc ccgagcccaa gccaggaggg atttccctta ggcaacacca 180
tcccagggag atctgccaca atttgcgttt cacagctraa gacgccgagg cttagagagc 240
tcgacctcct caaggtcaca ccactgggta aatagaggga tgcagactca ggttttgcta 300
tgtgctcaca tttcaacttt atgcttaaca tgaatggaaa aatatgaaag taaatagtga 360
aaaggtgagt tatgagctta gattacctag attattccag tatcccatgg aagctgagga 420
cttattccgc tttccacacc gaacactaaa tgtggaccag tatcaagaac cctcctgtcc 480
ccacgcagnt anaacccagt ggcttct 507

<210> 20
<211> 410
<212> DNA
<213> Homo sapiens

<400> 20
ggcagagcca aaagagggtt cttggatctc acgcaacaaa gagttcgggg cgagtccata 60
gagtaaagtg aaagcaagtt catcaagaaa gcaaaggaat aaagaatgcc tactccatag 120
gcagagcagt ggctttggct gctcagctgc ttgtacttgt tacttcttga gtatatgcta 180
aacaagggat tgattactcc ttgtttagca gttttctggg aaaggagtgg gcaattccca 240
gaactgaggg ttcctcccct ttttaagacc atattagggt gacttcctga tgttgccatg 300
gcatttgtaa actgtcatgg cgctrtgggw gtgtctttta gcatgctaat gctttataat 360
tagcgtataa tgagcagtga ggacaaccag aggtcactct tgtctgtgcc 410

<210> 21
<211> 496
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (36)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (356)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (443)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (454)
<223> n equals a,t,g, or c

<400> 21
ggcacgaggg cacsmkcaaa ccttgtcttc cctctnctgt tgcatccttt ccctaccctt 60
ccctcccagg tgctcggtac tttaccwagt ttctatatat cagtgtttta tgttggaatt 120
tttccttgtt tttattttac tagttggtaa accctgttta tgctgaaaca aataaggaaa 180
tggtatattt gaccatatgt gttattcata gaagacagta tgatcaaatg tgccaaaaac 240
aagcaaacaa aacttaattc ctgrgaagta tgccttattt ttattgatct gctttgtctt 300
acaattaagg tccaagagct tggttaaact gtattatttg cctaagtata aaaganaact 360
tgaactgcat tgcaatattg acgttcttta aaatgagaga cactgtcaag taatttaatc 420
cagagatcag ccaccagatt tgnaatgcct atgnatgtgt gtgtgttggg agtggttttt 480
tcctttaaac caccca 496

<210> 22
<211> 363
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (313)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (333)
<223> n equals a,t,g, or c

<400> 22
ggcacgagta taaatgatgg tgtggatgtc agggtgaggg aggagacaaa accacgatga 60
cccctagctt tgtggcctga actgtgggtg gctgagggga tcgttaattg aatggggcag 120
actgaggctt gtraggaaga tcagagtctg gttcttgaca tgagatgccc ttcaaacatc 180
tcttcactca ggtgcaacta gggatacaga aacactgkat atttcaacag cagaaattga 240
atggggggat tgatagcsct ggcgagggaa gcagctggta aagaagacag atggcaccct 300
gagacagccc agnggtggaa taggaccccc agngtgcagg gattaaagtt ccatgggttg 360
gtg 363

<210> 23
<211> 239

<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (238)
<223> n equals a,t,g, or c

<400> 23
ctcaggctgc tgcacgtggs catccgcatc cggcctttyt tcgacagttt gaccgtggag 60
agcgcggacc tgcagggctg ctgctttgct gggcctggca gcccccaccc gagaagatgg 120
agttccggac ggcatctatc cgcctctttg ggcacttaac aaggtctgcc acggagactg 180
taaggacgtc ttcctggacc aagtggtggg cgggctggcg ccctgctgct gcacctgna 239

<210> 24
<211> 461
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (426)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (428)
<223> n equals a,t,g, or c

<400> 24
aacaattaag tctttaggaa tgtgtaacca gaactatgtt agtattgctt ataaaacttt 60
agttaggttc aatatataca tatatacatc tctatatagg tatatagatt tgcattttgt 120
cttgtaaaat tttatttgaa taaattcttc ctgtaggtaa tgggaaacaa aattaatagt 180
tcatatgtca ctcatagcat ttctatattt gaaagtagcc caatataaaa cttttgattc 240
taaaattaaa ccagcagcct attacaagca cattctttga ttgagtcatt ggttataaac 300
ttactaaatg cagrgraagc agccaattta gggaaacttc tgagttggtg gggacactgt 360
tggattaata atgtacggta tgaattaagt gatgccttaa cttggatttt acatttaag 420
gttaangngg gggcatatgg tcagccaact tagggggcat t 461

<210> 25
<211> 453
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (442)
<223> n equals a,t,g, or c

<400> 25
accagaccaa ccctatgaat ggctttcata taaacaggtt gcagaattgt cggagtgcat 60

aggctcagca ctgatccaga agggcttcaa gactgcccca gatcagttca ttggcatctt 120
tgctcaaaat agacctgagt gggtgattat tgaacaagga tgctttgctt attcgatggt 180
gatcgttcca ctttatgata ccccttggaa tgaagccatc acgtacatag tcaacaaagc 240
tgaactctct ctggtttttg ttgacaagcc agagaaggcc aaactcttat tagagggtgt 300
agaaaataag ttaataccag gccttaaaat catagttgtc atggatgcct acggmagtaa 360
ctggtggaac gaggccagag gtgtggggtg gaagtcacca gcatgaaggc gatggaggac 420
ctgggaagag ccaacagacg gnagcccaag cct 453

<210> 26
<211> 1940
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (576)
<223> n equals a,t,g, or c

<400> 26
ggcagaggtc ctcagtgcag ggcaacagga ctttaggttc aagatggtga ctgcagccat 60
gctgctacag tgctgcccag tgcttgcccg gggccccaca agcctcctag gcaaggtggt 120
taagactcac cagttcctgt ttggtattgg acgctgtccc atcctggcta cccaaggacc 180
aaactgttct caaatccacc ttaaggcaac aaaggctgga ggagattctc catcttgggc 240
gaagggccac tgtcccttca tgctgtcgga actccaggat gggaagagca agattgtgca 300
gaaggcagcc ccagaagtcc aggaagatgt gaaggctttc aagacagatc tgcctagctc 360
cctggtctca gtcagcctaa ggaagccatt ttccggtccc caggagcagg agcagatctc 420
tgggaaggtc acacacctga ttcagaacaa tatgcctgga aactatgtct tcagttatga 480
ccagtttttc agggacaaga tcatggagaa gaaacaggat cacacctacc gtgtgttcaa 540
gactgtgaac cgctgggctg atgcatatcc ctttgnccca acatttctct gaggcatctg 600
tggcctcaaa ggatgtgtcc gtctggtgta gtaatgatta cctggggcat gagccgacac 660
cctcaggtct tgcaagccac acaggagacc ctgcagcgtc atggtgctgg agctggtggc 720
acccgcaaca tctcaggcac cagtaagttt catgtggagc ttgagcagga gctggctgag 780
ctgcaccaga aggactcagc cctgctcttc tcctcctgct ttgttgccaa tgactctact 840
ctcttcacct tggccaagat cctgccaggg tgcgagattt actcagacgc aggcaaccat 900
gcttccatga tccaaggtat ccgtaacagt ggagcagcca agtttgtctt caggcacaat 960
gaccctgacc acctaaagaa acttctagag aagtctaacc ctaagatacc caaaattgtg 1020
gcctttgaga ctgtccactc catggatggt gccatctgtc ccctcgagga gttgtgtgat 1080
gtgtcccacc agtatggggc cctgaccttc gtggatgagg tccatgctgt aggactgtat 1140
gggtcccggg gcgctgggat tggggagcgt gatggaatta tgcataagat tgacatcatc 1200
tctggaactc ttggcaaggc ctttggctgt gtgggcggct acattgccag cacccgtgac 1260
ttggtggaca tggtgcgctc ctatgctgca ggcttcatct ttaccacttc tctgcccccc 1320
atggtgctct ctggagctct agaatctgtg cggctgctca agggagagga gggccaagcc 1380
ctgaggcgag cccaccagcg caatgtcaag cacatgcgcc actactcatg gacaggggcc 1440
ttcctgtcat cccctgcccc agccacatca tccccatccg ggtgggcaat gcagcactca 1500
acagcaagct ctgtgatctc ctgctctcca agcatggcat ctatgtgcag gccatcaact 1560
acccaactgt cccccggggt gaagagctcc tgcgcttggm accctccccc caccacagcc 1620
ctcagatgat ggaagatttt gtggagaagc tgctgctggc ttggactgcg gtggggctgc 1680
ccctccagga tgtgtctgtg gctgcctgca atttctgtcg ccgtcctgta cactttgagc 1740
tcatgagtga gtgggaacgt tcctacttcg ggaacatggg gccccagtat gtcaccacct 1800
atgcctgaga agccagctgc ctaggattca caccccacct gcgcttcact tgggtccagg 1860
cctactcctg tcttctgctt tgttgtgtgc ctctagctga attgagccta aaaataaagc 1920

acaaaccaca gcaaaaaaaa 1940

<210> 27
<211> 864
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (552)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (773)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (856)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (863)
<223> n equals a,t,g, or c

<400> 27
tctaaatcca ttacaaatct gcttagcttc taaatatttc atcaatgagg aaatcccagc 60
cctacaactt cggaacagtg aaatattagt ccagggatcc agtgagagac acagaagtgc 120
tagaagccag tgctcgtgaa ctaaggagaa aaagaacaga caagggaaca gcctggacat 180
ggcatcagag atccacatga caggcccaat gtgcctcatt gagaacacta atgggcgact 240
gatggcgaat ccagaagctc tgaagatcct ttctgccatt acacagccta tggtggtggt 300
ggcaattgtg ggcctctacc gcacaggcaa atcctacctg atgaacaagc tggctggaaa 360
gaaaaagggc ttctctctgg gctccacggt gcagtctcac actaaaggar tctggatgtg 420
gtgtgtgccc caccccaaga agccaggcca catcctagtt ctgctggaca ccgagggtct 480
gggagatgta gagaagggtg acaaccagaa tgactcctgg atcttcgccc tggccgtcct 540
cctgarcagc ancttcrtgt acaatagcat aggaaccatt aaccagcagg ccatggacca 600
actgcactat caatctcggt cctgaacctc acctccaaaa agaaagcgac ttcagtagaa 660
agtggggtca gaaggaagag tgtggtcctg gcccagctag acaaaaagcg ggatgacttt 720
tgtaaacaga atcaggaagc atcatcagat cgttgctcag ctttacttca ggncattttc 780
agtcctctag aagaagaagt gaagggcggg gaattttatt tcgaaaacca agggggggtaa 840
ccgtctctgt tattcnagaa agnt 864

<210> 28
<211> 703
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature

<222> (549)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (612)
<223> n equals a,t,g, or c

<400> 28
gggtcgaccc acgcgtccgc caggagtagg tcctatcagt gcccccccag agtagagagc 60
aataagagcc cagcccagtg cagtcccggc tgtgttttcc tacctggtga tcagaagtgt 120
ctggtttgct tggctgccca tttgcctctt gagtgggcag ccctgggctt gggcccctcc 180
ctccggccct cagtgttggc tctgcagaag ctctggggtt cccttcaagt gcacgagggg 240
ttaggctgct gtccctgagt cctccattct gtactggggg gctggctagg acctggggct 300
gtggcctctc agggggcagc ctctccatgg caggcatccc tgccttgggc tgccctcccc 360
cagacccctg accacccccct gggtcctgtc ccccaccaga gccccagctc ctgtctgtgg 420
gggagccatc acggtgttcg tgcagtccat agcgcttctc aatgtgtgtc acccggaacc 480
tgggaggga gggaacactg gggtttagga ccacaactca gaggctgctt ggccctcccc 540
tctgaccang cttatcctga gtttggtggc tacttccctc tggcctaagg taggggaggc 600
cttctcagat tntgggggca cattgtgtag cctgacttct gcaggagctc ccaattccag 660
gaaggaaaag agccaaggcc ccacttttgg ggatcagggt ggg 703

<210> 29
<211> 337
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (71)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (331)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (332)
<223> n equals a,t,g, or c

<400> 29
aggtgacact atagaaggta cgcctgcagg taccggatcc ggaattcccg ggtcgaccca 60
cgcgtccgca nttacattta tgtttgtagt tctaagtaag accctgagag attttcaaaa 120
aggaattaat gattattttt gtcttcccca ggattggaac gagttactat gctgtttctg 180
ggattgcata atgttcgtca gacctccatg ttccctcgtg atcccaaacg actcactcct 240
taaattcaca ctttgccact taactccagt gtggatgaca gagcgagacc ctgcctcaaa 300
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa nncccccc 337

<210> 30

<211> 631
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (524)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (608)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (615)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (630)
<223> n equals a,t,g, or c

<400> 30
agggaactca ctgtggtttt ratttgtatt tyctttttta agtgaaagca rgkttattaa 60
gaaagcaaag gaataaagaa tggctattcc ataggcagag cccattgcca ctcagctgct 120
tatacttatt gttacttctt gattgtatgc taaacaaggg gtggattatt catgagtttt 180
atgggaaagg ggtgggcagt atctggaact gagggtttct cccctttgta gaccatacag 240
ggcaacttcc tgacgttgcc atggtatctg gaaactgtca tggtgctggt ggaagtgtct 300
tttagcatgc tgatgcatta taattagagt ataatgaata gtaaggacaa ccagaggtca 360
ctttcatcgc catcttggtt ttggtcagct tctttactgc agcctgtttc atcattaagg 420
tctttattac ctgtatcttg tgccgacctc ctgtctcatc ctgtgactta gaatgcctaa 480
cctcctggga atgtagccca gtgggtctca gccttatttt actncacccc ctaattcaag 540
atgggagttt ctctgggttt cagacaaccc ctggacatgt tttccccccct cccttttttac 600
agcagaancc ttaantccca acagtcgtan a 631

<210> 31
<211> 571
<212> DNA
<213> Homo sapiens

<400> 31
gaattcggca cgagtcccac cagcccccca aaaaacctct cagtagtttc tttcagtgta 60
caaaatgatg agcatttttc tatgatgagg ttttaaccat tattcagggt ggtcttttgt 120
ttttaaatct ttttttaact aataagattt acggtgtgta ttttatacag aaatgcatta 180
taaatgtttt taattgtgtt ctgtttttttg cagtctttaa gtgccatgcc aattgttctt 240
atattctata gaagttcgct caaaatactc aacaggggaa taggcagcgg acagtcagaa 300
tggttggaat tttggctttc taagaaaaac tttattttgc ataagcatgt ggtcagatca 360
ttttgtgcat atgcagcctg gattggatgt taagtaaatg cttgttcagt gccggtacat 420
ttacttaaat ctgtttttat ttttgtcatg tagaatacta ctgtggtcat cataatgtaa 480

tctatttctg tacctttttt tttttttttt actttgaagt cttaaataaa atgtataata 540
cccaaaaaaa aaaaaaaaaa aaaaaaaaaa a 571

<210> 32
<211> 424
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (413)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (414)
<223> n equals a,t,g, or c

<400> 32
tttctaaaaa tcaggaaaat tagttactaa aaattgctga tcatttttgt ttcattattt 60
ttgttatttc aaatgtataa gctctgggat tctttttgga gcaataccta caaagtcagg 120
caccagaatg tgcctcagag ctgtgacatt tcaacatgat ggttttggtt tggtttggtt 180
ttgtgtcctt tttatttgca gtttttctg ttgcaacaga aagtggcttg gaagtcttag 240
gtggtatgta acaaattctt tttaaaaatt ttaaagcagt atttaagtat tcttaaatgt 300
gtaaattcat ttaatgtttt acttctaatt tcttgtatct tggctgtctg gttttattgc 360
atttttaaaa aaactgaacc attaagkaat tggaaatgaa tgaaggtgaa atnnctgaac 420
ctga 424

<210> 33
<211> 1626
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (525)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (542)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (562)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (607)

<223> n equals a,t,g, or c

<400> 33
ccacgcgtcc gacgcggcgc acgcggcagt cctgatggcc cggcatgggt taccgctgct 60
gcccctgctg tcgctcctgg tcggcgcgtg gctcaagcta ggaaatggac aggctactag 120
catggtccaa ctgcagggtg ggagattcct gatgggaaca aattctccag acagcagaga 180
tggtgaaggg cctgtgcggg aggcgacagt gaaacccttt gccatcgaca tatttcctgt 240
caccaacaaa gatttcaggg attttgtcag ggagaaaaag tatcggacag aagctgagat 300
gtttggatgg agctttgtct ttgaggactt tgtctctgat gagctgagaa acaaagccac 360
ccagccaatg aagtctgtac tctggtggct tccagtggaa aaggcatttt ggaggcagcc 420
tgcaggtcct ggctctggca tccgagagag actggagcac ccagtgttac acgtgagctg 480
gratgacgcc cgtgcctaat gtgcytkgsg ggggraaacg actgncccac sggagggaag 540
antggggagt ttttccgccc gnagggggc ttgaarggtc caagtttacc ccatgggggg 600
aactggnttc cagccaaacc gcaccaacct gtggcaggga aagttcccca agggagacaa 660
agctgaggat ggcttccatg gagtctcccc agtgaatgct ttccccgccc agaacaacta 720
cgggctctat gacctcctgg ggaacgtgtg ggagtggaca gcatcaccgt accaggctgc 780
tgagcaggac atgcgcgtcc tccgggggc atcctggatc gacacagctg atggctctgc 840
caatcaccgg gcccgggtca ccaccaggat gggcaacact ccagattcag cctcagacaa 900
cctcggtttc cgctgtgctg cagacgcagg ccggccgcca ggggagctgt aagcagccgg 960
gtggtgacaa ggagaaaagc cttctagggt cactgtcatt ccctggccat gttgcaaaca 1020
gcgcaattcc aagctcgaga gcttcagcct caggaaagaa cttccccttc cctgtctccc 1080
atccctctgt ggcaggcgcc tctcaccagg gcaggagagg actcagcctc ctgtgttttg 1140
gagaaggggc ccaatgtgtg ttgacgatgg ctgggggcca ggtgtttctg ttagaggcca 1200
agtattattg acacaggatt gcaaacacac aaacaattgg aacagagcac tctgaaaggc 1260
catttttaa gcattttaaa atctattctc tccccctttc tccctggatg attcaggaag 1320
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ggaaggagaa tgctttcttt gtggcctcat ctgtggtttc gtgtccctct gaaggaaact 1440
agtttccact gtgtaacagg cagacatgta actatttaaa gcacagttca gtcctaaaag 1500
ggtctgggag aaccagatga tgtactaggt gaagcattgc attgtgggaa tcacaaagca 1560
aatagtactc cagaaagacc ctgtctcaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620
aaaaaa 1626

<210> 34
<211> 450
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (291)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (382)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (404)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (439)
<223> n equals a,t,g, or c

<400> 34
acccacgcgt ccgccggcgc ggtctatggc tgcgacttct ctaatgtctg ctttggctgc 60
ccggctgctg cagcccgcgc acagctgctc ccttcgcctt cgccctttcc acctcgcggc 120
agttcgrgga akctctccct aggtcaggtt ggagtgcagt gctgcaatca cggcttactg 180
cagccttgac ctcctgggct caagtgatcc tcccacctca gcttaaatga agctgttgtc 240
atttctggaa ggaaactggc ccagcagatc aagcaagaag tgcggcaaga ngtagaagat 300
ggggtgggct ccaggcaaca aacggccaca cctgaatgtt gatcccgggt tggcgaaaaa 360
tccctgcaag tcactcctaa tntcctccaa caaaaacaaa gggnaagttg caatttgttg 420
ggaaatccac cagttgaana acaatttttt 450

<210> 35
<211> 960
<212> DNA
<213> Homo sapiens

<400> 35
attttttttt tttttttttt tttttttaaa acaacttctc aaatttattt aactcatgtg 60
gttaacatgg tattgtataa aaagaaaaaa aaaacaccac tcaatactta ctaagccttg 120
cagacagctc agagttgagg cagcatattg ggcatagaga tcataggatt tgtattatcc 180
cttgcaagat ggaactccaa ccaacaccag aattttccaa ttcaaattca gttttagtcg 240
agaccccagc ataattttta gaaaaaagat tggattgttg cttttctttt aattttccat 300
tcctatttag acaaatgacc agaggcaatg acaaaagtaa ctgtttaaaa gggatttctc 360
tccagaagtt ttttctaaag gtttaagtcc aggctttcca tccttctctc catccttttt 420
cattttaaaa agaagggttt tggratwtgt caacctttac tcagcttgct atacaaagcc 480
actgctttag tcctagacat aatgccagga ctcatctccc aaacttctgg tcttaatcaa 540
gttcatgctt ggttgctaaa gaagctcatg ttaatcccaa agtcagcaca atcccaacct 600
taaaaagcag acagcctgat tgcatcactt acgacataca ccatcttgag gcaaaagaag 660
ccagtcagac accccttgtc tgctacgtgt gagacacatc agcagttgag cctgacccct 720
tccgcagagc tcactgtgca aaatcaccag cacaccactg caatccactg agctcaccgc 780
ctgtccagcc ataatggaag tcacttgaag gttatcattg taatagatga ttttccataa 840
gtaactaata aaaatgtttt ctttgatgtt tagacctact aacaattcag tctctccctc 900
tccatcctct cttagggagc ctgtactttt aagcaaatag ggaagctaaa acctcgtgcc 960

<210> 36
<211> 530
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (78)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (362)
<223> n equals a,t,g, or c

<400> 36
taacaattca atatataatt acacaaataa tttttaaata taatcaatag taaagactgt 60
tctgtggatg gtagtgtnta atacattttc tattttgtac agtgatttta ggccaaacag 120
ctgctgattt taagaaaaca aaaggcctga aacccgtctt cgtgtctcct ccctccctcg 180
ccttcctcct tcctagctcc tctcctccag ggccagactg agcccaggtt gatttcaggc 240
ggacaccaat agactccaca gcagctccag gagcccagac accggcggcc agaagcaagg 300
ctaggagctg ctgcagccat gtcggccctc agcctcctca ttctgggcct gctcacggca 360
knccacctgc cagctgtcag caaggcctgg ggaacttcag ccctggatgc agggccttat 420
cgcggtggcc gtgttcctgg tcctcgttgc aatcgccttt gcagtcaacc acttctggtg 480
ccaggaggag ccggagmtgg gagtcctggt ggggaacaga ttggaaggta 530

<210> 37
<211> 538
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (41)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (502)
<223> n equals a,t,g, or c

<400> 37
gccgcggcca cggggcgcag gggccatggt gcgcggcagg ntcttccggc tctcggtccg 60
ggacgtgcgc ttccccacgt cgcttggggg ccacggcgcg gacgccatgc acacggaccc 120
tgactactca gctgcctatg tcgtcataga aactgatgca gaagatggaa tcaaggggtg 180
tggaattacc ttcactctgg graaaggcac trwagttgtt gtctgtsctg tgaatgccct 240
cgcccaccat gtgctcaaca aggacctcaa ggacattgtt ggtgacttca gaggcttcta 300
taggcagctc acaagtgatg ggcagctcag atggattggt ccagaaaagg gcgtggtgca 360
cctggcgaca sggccgtcct aaacgcggtg tgggacttgt gggccaagca ggagggaaag 420
cctgtctgga attacttgtg gacatggatc ccaggacgct ggtatcctgc atagatttca 480
ggtacatcac tgatgtcctg antgaggagg atgccctaga aatactgcag aaagtcaa 538

<210> 38
<211> 1256
<212> DNA
<213> Homo sapiens

<400> 38
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ggtgcagaat tagtattgct tccttctttc tgtgtgtgat aatggtgggg gaaggctagt 180
accatctctg tcatacatca aattcccata tgtgaataaa tttatgtatt tttactgcac 240
tctttttata ggtttatcat tcctgcacca acaacgaatg ccattattaa aactttatag 300

aaagtctcaa tatatggcac agtgcttcat ttcttttttt catctagagt gccttagcca 360
ttcttggctt tctgccgttc cacaaatagc aatgtaaatt tgtcagtata atagagaatc 420
cacttatatt tcttcaacag ctattgggaa tatggttggg attacttcaa ctctatgtat 480
caatttgagg agaattgata tctttataag attaatccaa atcacagcat gtcaaaattt 540
ccttattagg gtagttttaa tgtccttcaa aaacactgta ttttcttcat atagatctaa 600
gaaaactttg gtgtttattc ctaagaaatt tatagttctt gttttgtaaa tgatatctat 660
tcttaagtta cacttaaact tatttgttgc tgtatataga aatggaattg acttctatgt 720
acagcagttg caaactgata ttcatatgca gaaagtgaaa ctagacccct aatggataaa 780
agacttaaat gtaagacctg aaagtatgaa actactagaa gaaaacatat gggaaacact 840
tcagtatcct ggcctgggtg aagattttat ggagaaaacc tcaaaagcat aggcaacaaa 900
agcaaaaatg gacaaatagg attatatcaa actaaaaaga ttcagcacag taaaataaat 960
aatcwataga gtgaagagac aaccttcaga agatatttgc aaactattca tctgacaagg 1020
gattaatatt tagaacatac aaggacctca aacaactgag caacaacaac aaaaatatcc 1080
aattttaaaa atgggcgaaa gagccaaata aacatctctg aaaaccagac gcaagtggcc 1140
aacaggtata tgaaaaaaaa aaatgctgaa caccgctaat catcagggaa atgcaaacca 1200
ataccacaat gagatattat ctcattwtgg ctattatcaa aaaaaaaaaa aaaaaa 1256

<210> 39
<211> 666
<212> DNA
<213> Homo sapiens

<400> 39
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gggggagggg ggcctcgacg gtttcccatc cccctctggc aaccctaatc ttccttctcc 120
atctgggccc tggggcgtct tccaccaccc aggccggatg ctttaaaaaa aattgctttt 180
taaagtgtct gtcgttgaaa gaaattagtc ttacccttga agtcargggc gcgtcctcgc 240
aatacacatc ttgttaggga aagtgttcgg ctccagctak ggttctacaa ggcgtttctt 300
gttcaccgcc ggagggaagc aggctccgga gtgactgcct tctgaaagtc ggtcttgtaa 360
caattggatg ratgcctttg aagagcccct gtccctattc tatgcttgaa aacagcgtgc 420
agtcctaatg ttcaagaacc acgaccacat aaaaacattg ctccccttct gctgctttga 480
aaacgacccc taaattccgt gtagaagttg ccaggtcgtc ttgacgtaca cttcgtttgt 540
atgatgtttg tctgtcaaat actgtgatgg aagagtgtat gcgggggagg agcagggaat 600
ttttaaaarc attttccggk cacctcagac tgggagatca tgttctttcc tgaaaaaaaa 660
aaaaaa 666

<210> 40
<211> 1016
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (6)
<223> n equals a,t,g, or c

<400> 40
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ccccgagcag aagggcctga cgtaccaccg catcgtagag gctttccggt ttgcctacgc 120
caagaggacc ctgcttgggg accccaagtt tgtggatgtg actgaggtgg tccgcaacat 180
gacctccgag ttcttcgctg cccagctccg ggcccagatc tctgacgaca ccactcaccc 240

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gatctcctac tacaagcccg agttctacac gccggatgac gggggcactg ytcacctgtc 300
tgtcgtcgca raggacggca gtgctgtgtc cgccaccagc accatcaacc tctactttgg 360
ctccaaggtc cgctccccgg tcagcgggat cctgttcaat aatgaaatgg acgacttcag 420
ctctcccagc atcaccaacg agtttggggt accccctcac ctgccaattt catccagcca 480
gggaagcagc cgctctcgtc catgtgcccg acgatcatgg tgggccagga cggccaggtc 540
cggatggtgg tgggagctgc tgggggcaca cagatcacca cggccactgc actggccatc 600
atctacaacc tctggttcgg ctatgacgtg aagcgggccg tggaggagcc ccggctgcac 660
aaccagcttc tgcccaacgt cacgacagtg gagagaaaca ttgaccaggc agtgactgca 720
gccctggaga cccggcacca tcacacccag atcgcgtcca ccttcatcgc tgtggtgcaa 780
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caccaggacc aggaagggga ctctggggga ccggcttccc ctgtraagca gcagagcagc 960
acaataaatg aggccactgt gccaggctcc aggtgcctcc ctggcytgtc tcccca     1016
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<210> 41
<211> 423
<212> DNA
<213> Homo sapiens

<400> 41

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agtgagctgt gattgcaaca ctgcacttca gcgtgggcaa cagagtgaga tcttgtctca 60
aaaaaaagaa ataatactag tttttgtttk tagattttgt atcctgaaac tttactgaat 120
gtttttagt tcgaacagtt tttttggtgg agtctttagg attttctcta cttatgatcg 180
tgtcatctgt aaacagagac agttaacttc ctcctttccr atttagatgc cttttctttc 240
tcttgcctaa ttgcctaatt acagcatgtt cctattctgt aaatgttcaa tgaactagar 300
aatgattctt gggtagttaa tattgtcaat gttgatgaac tcttttcctt cgctgaaagc 360
agctactttg ttggaggttt caattctgcg tggcaatttg cagcatttct agtggtactg 420
ctc                                                               423
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<210> 42
<211> 961
<212> DNA
<213> Homo sapiens

<400> 42

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gcctctacca cctcagttac agacaccacc aaggtcaaac agtgtatttg ctgtcaacca 60
agctgtgtca ccaaactttt cacaaggatc tgccataata attgcctctc cagtccagcc 120
tgtactccaa ggaatggtag ggatgatccc agtatctgtg gttggacaga atggaaataa 180
cttttctact cctcctcggc aggttcttca tatgcctttg acagcacctg tatgcaatag 240
aagtatccct caattccccg tccctccaaa atctcagaag gctcagggac taagaaacaa 300
gccttgtata ggaraacaag taaataattt ggtggattcg tcaggtcatt cagttggatg 360
tcatgcacaa aaaactgaag tttctgacaa aagtattgcc acagatcttg ggaaaaaatc 420
agaagaaacc acagttccct tcccagaaga gagtatagtt ccagctgcta aaccatgcca 480
cagacgtgta ctctgtttcg acagcactac tgctcctgtg gcaaatacgc aggggccaaa 540
ccataagrtg gtgtcccaaa acaaagaaag gaatgcagtc tcttttccta atcttgactc 600
acccaatgtg tcctccacct taaaaccccc ttctaataat gctatcaaaa gagagaaaga 660
gaagcctcct ctgcctaaga ttttatctaa atcggaaagt gccattagcc ggcataccac 720
cataagagaa actcaatcag aaaagaaagt ttcaccaaca gaaattgtgc ttgaatcttt 780
ccataaagca acagctaata aggagaatga attatgcagc gatgtaggaa agacagaaaa 840
atccagaaaa ttcaaaacta tctattgggc agcaaaatgg gggtttgcga agtgagaaat 900
ctatagcttc actgcaagaa atgaccaaaa aacaaggcac atcttcaaac aataaaaatg 960
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t 961

<210> 43
<211> 545
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (12)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (34)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (142)
<223> n equals a,t,g, or c

<400> 43
ccaccgcggt gncgaccgct ctagaactag tggntccccc gggctgcagg aattcggcac 60
gagttggagt cctttgctgt tcccaatttg tggaagagtg aagacatcac ccaaatcgtg 120
gccaactatg ggctcatatg tnttactcgg gctggaaatg atgctcagaa gtttatctat 180
gaatcggatg tgctgtggaa acaccggagc aacattcacg tggtgaatga atggwtcgct 240
aatgacatct catccacaaa aatccggaga gccctcagaa ggggccagag cattcgctac 300
ttggtaccag atcttgtcca agaatacatt gaaaagcata atttgtacag ctctgagagt 360
gaagacagga atgctggggt catcctggcc cctttgcaga gaaacactgc agaagctaag 420
acataggaat tctacagcat gatatttcag acttcccatt tggggatctg aaacaatctg 480
ggagttaata actggggaaa gaagttgtga tctgttgcct aaactaaagc ttaaaagttt 540
agtaa 545

<210> 44
<211> 377
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (301)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (347)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (359)
<223> n equals a,t,g, or c

<400> 44
cgatcacccc cgaaccattt catcacgtat tcttcagtgg ctggacgagg agctgcccga 60
cctgtccgtg tctcgcagaa gtagccactt gcactggggc attccggtgc ccggggatga 120
ttcgcagacc atctatgtat ggctggatgc cctggtcaac tacctcactg taattggcta 180
cccaaatgct gagttcaaat cttggtggcc ggccactctc atatcatagg taaggacatt 240
ctcaaattcc atgccatcta ttggcctgcc ttcctgttar gggccggcat gagcccgcca 300
nagcgcatct gtgttccatt cccaatggaa cagtctgtgg gccaaanatg tccaagagnt 360
tgggcaagtg gtggatc 377

<210> 45
<211> 440
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (387)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (416)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (436)
<223> n equals a,t,g, or c

<400> 45
ttggacatcg tggccaactc tatcaagacc acaaatacca cttacaatta attttaaatt 60
attcatctgt acatagtttt ctaaaatgta tataattcaa acagagcatc ttgtaactga 120
agacacacca tatctatgat atcgcattag tccatgtggg gaaaagaaag atcagattgt 180
tactgtgtct gtgtagaaaa ggaagacata agaaactcca ttttgatctg tactaagaaa 240
aattgtttct gctttgagat gttgttagcc tataacttta gccccaactc tgtgctcaca 300
gaaacatgcg ctgtaatgga tcaaagttta atggatttag ggctgtgcag gatgtgcctt 360
gttaacaata tgtttggcag gcggtangcc ttgggtagaa gtcatcggcc attccnccat 420
tccccggttt aacccngggg 440

<210> 46
<211> 525
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (345)
<223> n equals a,t,g, or c

<400> 46
gtccggctgg gccgggacaa aagccggatc ccgggaagct accggctgct ggggtgctcc 60
ggattttscg gggttcgtcg ggcctgtgga agaagcgccg cgcaacggac ttcggcagag 120
gtagagcagg tctctctgca gccatgtcgg ccaaggcaat ttcagagcag acgggcaaag 180
aactccttta caagttcatc tgtaccacct cagccatcca gaatcggttc aagtatgctc 240
gggtcactcc tgacacagac tgggcccgct tgctgcagga ccacccctgg ctgctcagcc 300
araacttggt agtcaagcca gaccagcttg atcaaacgtc gtggnaaaac ttggtcttcg 360
ttggggttca acctcactct ggatggggtc aagtcctggg ttgaagccac ggttggggac 420
aggaagccac agttggcaag gccacaggct tcctcaagaa ctttctgaty gagccyttcg 480
tcccccacag tcaggytkag gagttctatg tctgcatcta tgcca 525

<210> 47
<211> 414
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (403)
<223> n equals a,t,g, or c

<400> 47
ttagaaagar agggggctgg gggccgagac ttctgggtcc ctgtatgttg cagagggttg 60
catgtcatct ccatggagaa ggctgtgtac gctgtcacgc aatcccttgt aagaggccag 120
gcccctgggg gaggagggag cagctgtggc tcacacagcc ccaggaaacc acctcttcct 180
tcagtgagtc agatagatag agaatcccgt gacagtgaca ggcaagtgac tagccagata 240
gaaagcattt ttgtgtaata actaattttt gtttgcttct ctctctctct tccccgccct 300
ccccatccgg attcccgtgg ctgtgtgcat ctcctgsctg tgtccccatg tctgcccgca 360
gtgcgcttct ccgagaaggt cactgtccat tcctgggtgt ctnggcaagg ccgg 414

<210> 48
<211> 323
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (11)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (274)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (321)
<223> n equals a,t,g, or c

<400> 48
tcgggtccgg nattcgccgg tgccggggac agaaacctcc tgccttctta gttcataacc 60
ccccccttaca ttagattcta accctgtggt gattttaggt tgggatttgg gcgcctgcag 120
atggctccga agccagcctc ttgtgatccg agccacttct ctggcactcg gagcgctggc 180
acccgcggag cccttggttc accggaccgc ctgggaacct ggccggggtc tctggcagcc 240
tcccagggct gaggttcaga ctctgttccg cctnacccag gtccacacct ggatagggct 300
gggagttgag gcttggtttt naa 323

<210> 49
<211> 841
<212> DNA
<213> Homo sapiens

<400> 49
tcgacccacg cgtccgsaga tttcagcctc acatactaag taaatactga taaataagga 60
aattagaaat ttagtattca taattaaata tgctctaaaa tttcckrtac ttttatttcc 120
tgtttattct taggtagatt ggaaggggga aacagtctgt tctccctaat taaatttttt 180
ctaataacga ttagtagaat atggacattc tatatgacag tgacattaaa agaggctctt 240
tggaagtata tacattatta acataatgtg tacaagtcct tttgaaatga caactttaat 300
gggtttcagc tcttttatct agagcttgag ataattcaag ctgagttttt cagggcatat 360
cacaacggca aagtgttcag cagtgggata tcaatgctta tttacatttt cctactgcta 420
tttatataaa atgttattcc attcagagga tgccttttat ccccacatta aagcacagat 480
cattaagcaa taaaaaccaa attgtctgtc attcaaatta taactgcagt tatttttgca 540
tggtaagagt gaggtgctaa ttttgtgtga gatgaacttt gtaaactact ttgggaaatg 600
ttctttggaa gtaaggtttt ttctccttta gtcttatgct tccacttttg tctcagattc 660
acaatccatt aaaamawggg gaaaaaagaa aargtaaaat tgagagactt ttgttagagg 720
agctatttgg aatgaaccaa cattycasat ttcccaaaat gtaagttagg aagtctccat 780
kgycyckgcc attaccaaaa tacactgkta ctatcttaat ctcaagagtg tcattacagt 840
g 841

<210> 50
<211> 534
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (423)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (430)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (524)
<223> n equals a,t,g, or c

<400> 50

aggaaattta gaaaatgatg aattcttgtc catttttgta atcaagattt taggaaaaac 60
agaagtacat ctatctttat gaaattttgg gcaggttttt gtgtatcaat attttgtact 120
tttagggaat attttatttt ttagttattt gtgtcaaatt ataattataa aaggtacagc 180
agaaaatata ccatgttttt atataggttc acacctgtac ttaggaggga ccctgtccat 240
ctatatactt tttgtataaa attttaaaat gttaaagatc cacaaggtct taataaaatg 300
attctatagc tagaaaaacc attaccttcc cagtggcttg cactaaaata tacctgggaa 360
aaggaaccta gaaagactgg taactaatgc ctggaaatgt tctatattga atgtaccatg 420
ccnctggttn gggaaaaatg tactaataat gggaatggga aataaaccca gaaatccgaa 480
gttaattcca gcctaaaaaa aaaaaaaaaa aaaagggggg gccnccccta gggg 534

<210> 51
<211> 317
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (222)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (250)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (265)
<223> n equals a,t,g, or c

<400> 51
ggcacaggaa aaagcacttt cttaagccta cagtatcaga tcaatgggga aaacaacaga 60
aaactaagag gagaattttc ccgttaattt tcttgcagaa aagtataagt ctaattgccc 120
attgccataa atttgtctt gtactcagag aagcaacatg cactggctca ttttatgtgc 180
aaagaaaaga tttcaccatt aaaaaaatta acttggctag gnatggtgtc tcacactggt 240
gaatcccagn cactttgggt ggctnaaggc agatagactg cttgaaaccc aggaattcaa 300
gaccagcctg ggacaac 317

<210> 52
<211> 1789
<212> DNA
<213> Homo sapiens

<400> 52
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tttcttacat tccacttttc tatcttttcc aaatattcca cagtgatcat gtattaattt 120
ttctcttatt ttgatgttgc aaatatttat tttattatgg aaaacggcaa gctacatatg 180
gggaaaaaga aaaattgaaa ttatgcaatg gcctaccact caagagataa ttattaagat 240
tgtggtgtac ttttttctat atactttttt ttaaaggaaa ggatcttact ctgtcgacca 300
gcccctcacc tcctttgact agctgggatg acagcacatg ccaccatatc caagtatttt 360
tgtatttttt gtagagaagg ggtttcatta tgttcaaact cctcagctgg cctgcttgat 420

ccgatgcttg ttagccttga catttacaat gaacacaagt gtgttgccat cttctgtctt 480
cttcacagac aacttagtag tcaggggaac ttgatgatgg ccaagtggtc aagctcctca 540
gggctgtctt ccgtggatac ttgagctgcc ccaggagcca cagcgtctca ggcagctgaa 600
aagtgagtga catgtagggt gtgtgtgtgt gtgtgtgtgt gtgtgtatgt gtgtgtgtgt 660
gtagctgtaa cacctcagcc ttgcctcctt ggccttcaca gcccttgctt tagctttggc 720
tttgagagag gcagaggctc cctcttttgc cctcactgtt atcttggtga aaagccagtt 780
tggcagtttc tttttttaaa aaaatgcaag tatcataatt cagcaatcac atttgggggc 840
aatttatccc agagaaaggg aaatttatgt tcacataaaa acctgaatta acttcaaggg 900
aatgttattt aacaaacagg ttttctcact taactgatta tattcttgat ggatacacaa 960
attaaatctt aatacaatat ctccagtgga tcctccaaag ttgtatctgt tttcatgggc 1020
cagaatgagg gaaagtcatt ctggccattc tcttttgcag agaaggtcat tctcttttct 1080
atatgaggag catctctcaa ctgcaaggtg cagctcaaat atctgtctat gtatagatac 1140
gactttcaaa gtctagatag gaatggcttg aacataccat ccacatttta tggaaaatcg 1200
cttgtttctc ttttcccctg tcttaatctg tttgtgctgt aaacaaaaca aaataccaga 1260
gactggataa tttataaaca gcaggagttt atttctcaca gtttcagagg ctgggaagtc 1320
caagatcaag gtgccggcag gcttggtgtc tagggaagga tcattcctta tagatggtac 1380
catctaggtg tcttcacatg gtaaagggaa ggaagggcaa acagggacct agttggtccc 1440
cgccagacct ttcataaggt cactagtccc actcatggag gctctacccc catgacttga 1500
ttttttccta aaggccccac ctcttgacac tgttgcattg aagattaaat ttcaacatga 1560
attttggagg gaatgcaaac attcaaacaa cagcactccc tcatctatag atttctacaa 1620
ctttcagatt attgcagcaa gtggttccat ctgtaaatca cttggctagc ttatgtgtgt 1680
tgtctctctt ccataacaca tcaacccaag atttccaaca aaagaataat aacttaaaac 1740
aacaacaaaa aaactcactc acacaaagta tgtgtataag caggttgta 1789

<210> 53
<211> 654
<212> DNA
<213> Homo sapiens

<400> 53
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aratggatgt tggcaaaata ggaggatacc ctcatttgct gaatggggga cctgctctga 120
gcctgcccag kggccaggcc tgctccaggt taaactggac ggaaggccca ggtctcagtt 180
tctttcaacc aggagaggcc gctgcctaga gcccctcccc accttttcct ggatgggtga 240
ggcaagccag gagagcaagc agtgttgtcc tcacgggagg aggactgagc gactgggaaa 300
actcggctct acatctcacc cagaacggct tttagaaaca ccacagctgg agagtcctgg 360
ctgagccttg ggagtttcag ctctttggcg gggtgcccag gtgccatgcg atcagcgaag 420
cctgcgagtt ggcaggactc tgaggtttcc tgcagaccat gccatgagat tgaaggtgcg 480
gggaaataaa gaaaaatcac catttaggag actccattct ttccctacaa cccagctgtg 540
gtcccagaga tcaggggtg ttgccaggtg tggctgggga agggtctggg ttcacaaact 600
caccggcact ctttagtccc cgtataacat ggtggttaag gataaagatc ttga 654

<210> 54
<211> 334
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (154)
<223> n equals a,t,g, or c

<400> 54
ggcacgtagg ggatgcccac cgccagtcaa agggttgggg gtggtctctg caccttaagt 60
actaacctgc cgcccacgcg cctcctgacc acagcacccc gtcggctttc taattctgtg 120
agctgccctc gtgggcgtgg cctccctgtg gagntcccca tgtgcctccc cttggtccag 180
cctgcagcta ggaagtgggt cacagcgacg gggctgggct gggccaggcc aggctccggg 240
agatgtggaa ttggcgaaac aactgcccca gtagtatcct ccgcctaggr ctccaagagg 300
tgggaattgg ggcactacgg ccgggtaagg cagt 334

<210> 55
<211> 474
<212> DNA
<213> Homo sapiens

<400> 55
tgcaaacatg atggatgggg aaagcatagt aactgtactc accaacaaga tgctggagtg 60
acctgctcag atggatccaa tttggaaatg aggctgacgc gtggagggaa tatgtgttct 120
ggaagaatag agatcaaatt ccaaggacgg tggggaacag tgtgtgatga taacttcaac 180
atagatcatg catctgtcat ttgtagacaa cttgaatgtg gaagtgctgt cagtttctct 240
ggttcatcta attttggara argctctgga ccaatctggt ttgatgatct tatatgcaac 300
ggaaatgagt cagctctctg gaactgcaaa catcaaggat ggggaaagca taactgtgat 360
catgctgarg atgctggakt gatttgctca aagggascag atctgacctg aractggtaa 420
tggagtcact gaatgttcag gaagattaga agtgagattc caaggagaat gggg 474

<210> 56
<211> 367
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (250)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (252)
<223> n equals a,t,g, or c

<400> 56
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gcacacggcc ttactatgct atcaattcca tatatggaaa ggtgttttcc ctttcagagc 120
tctttaaagc tctgcagaag atttacatgt gtttatagag ctaagagaaa tcagggcatg 180
gaaattgagt gtgtaataaa aattaaactc ttcatgttat ataatcatgc ataacttcta 240
tcttcattcn cnggaagttg cctagagcac catcacagct aggaagcttc catcatggat 300
taccttattt cccaaagcaa gtactccaat aattgtctca agagaggaag gacaactggt 360
taccagc 367

<210> 57
<211> 564
<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (542)
<223> n equals a,t,g, or c

<400> 57
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acatggaaca gagtgggact tctaattgta tgacttcaag attttgcttt gtttaaatta 120
ataactgttt tcagaattaa gtgcttaaaa acaaatttga ttgaaaagtt caagacaaga 180
attttgctct ctatggctgt tccatataaa tttgatggtt gattctgaat gtaaatgact 240
gaagaattaa aaaataagaa attccttttt aaaaggcatg cctcttgcac tgtgaacaag 300
acagtagtcc cttaaaccat gaatatgtca gtgttctatg gattacgaaa ttagtaatgt 360
tgcttagccc aaacgtgttt tttaaaaagt atagttttgt acatctcyaa gttatcaaac 420
ttcaaaattg agaacaaatt taaaagtcca tatatgcaac tctagtaagc acttaatagg 480
ttacatagca ctggttaaga acaattaatt ttgtttctat attattacta attattatta 540
cnaatcaaaa aacactgtga taag 564

<210> 58
<211> 444
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (358)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (382)
<223> n equals a,t,g, or c

<400> 58
ggcacgaggg aaaaccataa ctgcctctta atttaacata gaataataca tagttctgta 60
ttttttttaa agtgagctta atgggtaagt atttttata tgctttagct atagctaaag 120
aaaactgata cttaacaaag ttgaatagta ttattcactg gtgctcctaa aatattgttt 180
ttcagtgtaa aatatgcata tcttctatat ttaatatgaa agtcttgaaa tgtatcagac 240
agaagggkat ttcagtttgc aaataatgag caatgtagca attttaacac atttcataaa 300
tatatatttt gtcattggtg gagagcacca tttgttgttt tgaatatact ttaaaggnaa 360
gaggtacaag ggacataaat gntgagatta cctacaggat ggaaatagca gtacagttcc 420
attggtagat attttgaaat gttt 444

<210> 59
<211> 347
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature

<222> (327)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (328)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (340)
<223> n equals a,t,g, or c

<400> 59
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catcacagtg atttgtcatg aaaagccata tatgggggac atgctaaaat ggcttctgaa 120
tgaaatacga cagcagagaa agatgccact gaaatgctga aattatcttt gctgagcagc 180
ttttgaatgc taagggttcc agtatgtgac ccaaagaagg agttgtctca actccttggt 240
acagggttca ttcaaacccc caagctgtga gagtgtgttt atttttaatt ttttaaaagg 300
tatttaattt ccaaccacac ttcttanntt tttggaaaan gacaatt 347

<210> 60
<211> 322
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (245)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (321)
<223> n equals a,t,g, or c

<400> 60
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agaaaactga gtctgatgtt tgatttgtgt aaagacttct ttaacttttc taactcaatt 120
tttactaagt tataggacta ctcagatttt gtttcttttt tgctcaattt tggtcaattt 180
tgtttttgtc tatgtcacct aagtttycaa atgtattggc atgaatattt ycataatatt 240
ccctnattat cttttacatt tctggggtat cttagcggtg tttccctttt tatccctaaa 300
atgtttatcc atgctttctt nt 322

<210> 61
<211> 834
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature

<222> (793)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (810)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (814)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (834)
<223> n equals a,t,g, or c

<400> 61
gatatgatgc ccctccttca taattatgta acagttgata cagacacact tctgtctgac 60
accaagtatc ttgaaatgat atacagtatg tgcaaaaagg ttcttacagg agttgcagga 120
gaagatgcag agtgtcatgc agcaaaattg ttagaggtca tcattctgca gtgcaaaggg 180
cgtggcattg accagtgcat tcccttattc gtggaagcag ccttagaaag actgacaaga 240
gaggttaaga caagtgaact tcgaactatg tgtctgcaag ttgcaattgc agctttgtat 300
tataatccac acctactact cmatacctta gaaaatcttc gcttccctaa taatgttgaa 360
ccagttacma atcattttat tacacagtgg cttaatgatg ttggactgtt tcttggggct 420
tcatgacaga aagatgtgtg ttctcggact ctgtgctctt attgatatgg aacagatacc 480
ccaagtttta aatcaggttt cyggacagat tttgccggcy tttatccttt tatttaacgg 540
attgaaaaga gcatatgcct gccatgcaga acatgagaat gacagtgatg atgatgatga 600
agctgaagat gatgatgaaa ccgaggaact ggggagtgat gaaagatgat attgatgaaa 660
gatgggcaag aatatttgga gattctggct aagcaggctg gttgaaagat gggagattga 720
tgaaagattg ggaagaaaga tgatgctgaa agaaactgct ctggaaaggc tattcccaca 780
atcattgatg atnaaaaaat aaccctgttn gatnaatttc caaatatttt aaan 834

<210> 62
<211> 1796
<212> DNA
<213> Homo sapiens

<400> 62
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tactggaaac ttgcattatt tacagccatt aggagctccc tggcttccat tccactcatg 120
actagcttta cctctttgac ccactgtat tattgtctag cccagttcag ctgaatcttt 180
caacacaaaa tatacaggga accccttcct ggggaacttc ctttgttatt gaggtcttcg 240
ctgatggctt cttccatttg atactcagtc tcagtcacag taggattacg gaatcttttg 300
ccagagtatc aatctacatg ggtgctacac attactgaaa aaaattagga acatggtgct 360
agttaattca agtcttcatg taaaacttct tctatcatag tggacattaa aaaaaatctc 420
tctgcaaagt gcattgaccc tacctctagt agatgaatgt tgaacaagta gcctatctag 480
gaagcaagtg actagcatcc atgggcatcc cacaggttgt agtccagccc cgatcttggt 540
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ctggtgtctg gtacctgatt tttcaggatg ctgacattta cttcttgccc acaacaccat 660

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ataaaagaca aaagtttaat atcataataa aataagcaca tagtagcttt tagtaaatca 1680
ttgctgaatg aatgaataca tatatgaatt caaagcaatg aaaaaatcac cccaggaaaa 1740
gatgtaaaca tttgacatag gacaagtcac caaaaaaaaa aaaaaaaaaa ctcgta 1796

<210> 63
<211> 1376
<212> DNA
<213> Homo sapiens

<400> 63
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cacacataca tatcaggttg ttttctagtt aaaaacccaa gtagctcaga ttctacttta 120
atgtcagtgc agatttgcat tgaatcatgc cattatgttt tttctcattt ttatgctgtt 180
gggtcttagt ttttaaattg atataaagaa ctcagcaatg gttttatttt ctactcatac 240
ttagggttta ggaaacacta ccactagtta tcatttaatc aacttcaatg gtctactgaa 300
acaaaaatgg taacttttca ttagtggatt atttagagtt atagtagttg tttccagaaa 360
acacttcctc acaattgtac ttcccaatca aatcatgtga tcatacagtt attcccatga 420
aaggcagaat gtttgtttca aaattaatct agtttctgt acatttaaat ttgagaaggt 480
gacaactggc tcttttccag tcttccttca tgtcagtttt ctgatagacc actattggca 540
aacagtatct gtcaactacc aaatgtgtaa aattttctgt atttcacttt gtcttatttg 600
taaatagtga actaaaactt ttggcagatc agcaacattt gctgagcctg ttttttaagc 660
taatgtgtat tcttactaat gttcctatca agaatggatt tgtaatatat gctgtctatt 720
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gactactcag aaaattattt cacgtaattg tctaagaggt caatattttt taatgcatat 1320
tgaatcaaat aaagtgctct aaagaaatta ttctccaaat aaatttttaa aaaaaa 1376

<210> 64

<211> 574
<212> DNA
<213> Homo sapiens

<400> 64
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atcctctttt tttggtccct tctatttttc agtctccggc agcctcttgg tcatgaaagc 120
cctcagattg tcggcttccg ccctcttctg ccttctgctg atcaacgggt taggggcagc 180
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gccggggacg cagtgcccgg gccaaaggat ggcagcgccc cagaggtccg aggcgctcgg 300
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gcggtgctgc tgcaggcact cgaccgtccc gcctcacccc cggcaccaag cggctcccag 420
caggggccgg aggaagaagc agctgaagct ctgctgaccg agaccgtgcg cagccagacc 480
cacagcctcc cggcgccgga gagcccggag cccgcgtccg cctcgccctc agactccgga 540
gaatgggccc gaggcgagcg atccctccga ggag 574

<210> 65
<211> 603
<212> DNA
<213> Homo sapiens

<400> 65
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tgagagccga ataaggtttg cctgaaataa ctgacactat ataatttctg ctttggcaaa 120
tactaagttc taacttgtca ttcctggtag aacaagcttt atttttcgag cctagcaatg 180
atctagaagc agatgttatc tcagtgcctt ttgcaatttg ttgtgtgggt tttttttttt 240
ttaaagccac acaataattt tggaaaacaa tgtatgggta gaacatgtgt ctgttaattg 300
cacacaaaac cacttttaat gggtacagag ttaaatttga aggaataagt tcataatact 360
gaagctagaa ccaagcagaa tctgtttttt tctgaggagt atcggtagca taaatgtgat 420
tataaacata gtacacttga tatatggagg cagtgacagc tatttttaca aaatttaaat 480
ctgcaaatgg attcaacatg tttatgggtt attaaaattg tctgatttct taggttcttt 540
atagtacacg tgttgaaaat aaatgattaa gaattgtttc aagaaaaaaa aaaaaaaaaa 600
aaa 603

<210> 66
<211> 1772
<212> DNA
<213> Homo sapiens

<400> 66
tcgacccacg cgtccgggag gatccccagc cgggtcccaa gcctgtgcct gagcctgagc 60
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ttttgaaaca tcaaaaaaaa aaaaaaaaaa aa 1772

<210> 67
<211> 1829
<212> DNA
<213> Homo sapiens

<400> 67
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<210> 68
<211> 1688
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (912)
<223> n equals a,t,g, or c

<400> 68
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tcgttttgtt tgtttttgtt tcactgttca tcacagcagt gttatctcca ggagacatat 1500
agagagctca accggcaatc tcaggtgcat ttaacatttt taaaacgaaa cagtagttga 1560
ccaaattttt cttcttaaaa aattggaagt gggggggaatc caatgacaaa aactaatgtg 1620
gcttgtttct ggagaaaata attactgtaa atggaacaac aacaacaata aaacacacgt 1680
taaacatc 1688

<210> 69
<211> 565
<212> DNA

<213> Homo sapiens

<400> 69
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ctgaagatgt acctatggtc ctagtaggaa ataaatgtga tttgccttct agaacagtag 120
acacaaaaca ggctcaggac ttagcaagaa gttatggaat tccttttatt gaaacatcag 180
caaagacaag acagggtgtt gatgatgcct tctatacatt agttcgagaa attcgaaaac 240
ataaagaaaa gatgagcaaa gayggtaaaa agaagaaaaa gaagtcaaag acaaagtgtg 300
taattatgta aatacaattt gtactttttt cttaaggcat actagtacaa gtggtaattt 360
ttgtacatta cactaaatta ttagcatttg ttttagcatt acctaatttt tttcctgctc 420
catgcagact gttagctttt accttaaatg cttattttaa aatgacagtg gaagtttttt 480
tttcctctaa gtgccagtat tcccagagtt ttggtttttg aactagcaat gcctgtggaa 540
aaagaaactg gaatacctaa gattt 565

<210> 70
<211> 675
<212> DNA
<213> Homo sapiens

<400> 70
ccagcatcag aagttctgat ggatgatgac cttcagaaaa gtgtggatat gatcatggat 60
atgttttgtc ctccaggaat aaaaattgat gcatatccgt ggttggaatg cttcatcaag 120
tcatacaatg tcacaaatgg aacagataat caaatttgct atcagatttt tgacaccaca 180
gttgcagaag atgtaatcta atattgccat ccaatttagc atacataaaa tgttgccact 240
caccttccct gtttgagctt cttttcctga cctgagtttt gtatcagcaa tgttgatgat 300
gttagcatgg gtatgggatt agaaaatgtc cttaccttaa atctcttggc ttttactggg 360
tgcaaggtaa ataatggcta tggattttgt tttgctttct gttttgcttt tgtacaaaga 420
gacctgctta aacaagtact gctgagataa gtgtctgatc aagctacagt gtactttaag 480
tagaaatggc aaagttgctt tgttggggtg ctgatactga tgattttagg ataaattcat 540
ttctttaaac ttgtaataca tggttttatt gcttgtttct cyccaggata gtagagattt 600
ctctatttca cctcaamcta ataaaagtgg tcagatttat aatgttaaaa aaaaaaaaaa 660
aaaaaaaaaa aaaaa 675

<210> 71
<211> 270
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (247)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (260)
<223> n equals a,t,g, or c

<400> 71
ctgagatgcc acaagaagca gcacagtgat cagagtgaga acaagaactc agacttggtc 60
accttcccac cggaaagcgg tgcctcggga cagctcagca ccctggtctc cgtggggcag 120

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ctcgaggctc ccctagagcc cagccaagac ctctagctca gccgaagagg gtggtcagct 180
gtcggaactt ctgaccagtg ctgttgccca gccctccaga ggtgaggcca ctgagagaca 240
ggctttnggc accacttctn gggctggccg                                  270
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<210> 72
<211> 538
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (101)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (302)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (449)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (459)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (521)
<223> n equals a,t,g, or c

<400> 72

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tgtggctcag cctaccaaag tgctgggatt acaggcgtga ncaccatgct cggccagtca 120
gtatcatttt ttaaaaatgt agaacctggt ttgatgactc taattaaatt gtctgccaat 180
tactgaagag ctactacata ctagwttctg ggctttagtt ctaaagccca cagcaacctc 240
atgaataaat attattagcc ccactgtata gatgagataa cagactagga gggagaagtt 300
anggaaactt gcttaatgcc tcctgtttag aaaatagctg aactggaatt cagccctgtc 360
ttccatttca ccctgcctgt gtctcacgca cagaacaccc ggggatccgc tggttcccaa 420
agcactgatg agaaccctaa tttgtcaana ttcctgggnt ccagtaaatg gtggtccaga 480
atggtgggtg atctgatttc atattatctg ccaggtgaaa ngtttctgcc tggcaaaa   538
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<210> 73
<211> 1071
<212> DNA
<213> Homo sapiens

<220>

<221> misc feature
<222> (1010)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1048)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1062)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1066)
<223> n equals a,t,g, or c

<400> 73
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ggctcgctct gtcgccggcg cgggattggg gcgcgagggc catgggcgcg ctctcctaag 120
gcggaggtcg cgggcgggag gggaggaggc ccgagagagg ctgctgcgaa ggccgcgggc 180
ccgtgactgg gcgcgaggcg gccggcggcg gcggcggcac cagcaccacc atgtcgcgct 240
cagtgctgca gcccagtcag cagaagctgg cggagaagct caccatcctc aacgaccggg 300
gcgtcggcat gctcacccgc ctctacaaca tcaagaaggc atgtggagac cccaaggcaa 360
aaccatccta tcttatcgac aaaaacctgg aatctgctgt gaaattcata gtcagaaaat 420
tccctgctgt agaaacccgc aacaacaatc aacagcttgc acaactacag aaagaaaaat 480
cagagattct gaaaaatctg gcattatatt acttcacatt tgtagatgtt atggaattta 540
aggaccatgt ttgtgaattg ctgaatacta ttgacgtttg ccaagtcttc tttgatatta 600
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tgatactgct gtctcgaatt gaagaaagga aggcaatcat tggattatac aactatgccc 720
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cagatgcact aatttctctt caaatggtat atcctcgaag gaatctttca gctgaccagt 900
ggagaaatgc ccagttattg agcctcatca gtgcacctag tacaatgctt aatccagcac 960
agtccgacac tatgccttgt gaatacctct ctttgggatg caatgggaan attggattat 1020
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<210> 74
<211> 640
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (93)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (96)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (619)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (624)
<223> n equals a,t,g, or c

<400> 74
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tcataaatga ataaataaat aaataaataa tangtnacga tccattgtgg cttcctggaa 120
acatccatgt tcacagctgg ggtctggtca gtctgcatag tggagcacac tgctaggatg 180
catccttagc aagtgaaaaa agtgaggctc agaactgttt gtagagtata gccttttatc 240
taaggaaggc agatgaagac tggcttatga taaaggtgct aaccccccaga ctagtaaaaa 300
tggggttccc tgtggagtag ggaaggggca gtgttataag ttggatttct ggccatatct 360
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tgttcattgg ctggggctcc tggaacagaa gacagatttc caaagagaaa ggcacacmaa 480
tttatgtaat ataagtttwc catgacmtgg gagcctttat aaggaatgac cccaaggaaw 540
tggttaaacc tgagtggttt tgtgtaaggt tttaatgagc aatgaaaagc tatggggacc 600
tatgatagga ggatgtaanc taanccaatg acctggggga 640

<210> 75
<211> 507
<212> DNA
<213> Homo sapiens

<400> 75
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ttttccgttt ccacatagac aatcacataa tctgtaaata atgactctta cttttccact 120
ttagtcgtta ggttatacct atatatatat wwwmwtgctt tactggacta atttcaacct 180
ccagcacacc accaatgaat agcagtaata ccagcataat tgtctgcagt tctgctgaga 240
tacgtgctct attttattgg cttggctgta ggtttttatt ttattttttg aagaggctaa 300
tctcttacag gaaaggtttc tttttatatc cagtttttac atgatgaatg atttcccagt 360
atttcataat tcatgaggct gaattcctct tgaatttatt aaatgcttcc tgtgcatcct 420
ctgtgatgat catgtttatt tactgctaga actcaagtac ctagaactgt tcctggccaa 480
tgatggtatg taataaatac ttcaatg 507

<210> 76
<211> 1390
<212> DNA
<213> Homo sapiens

<400> 76
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cgctctaagt cctacttgaa caaacacatc cagaaggtgc atgtccgggc tctcgggggc 120
cccctggggg acctgggccc tgcccttggc tcacctttct ctcctcagca gaacatgtct 180

ctcctcgagt cctttgggtt tcagattgtt cagtcggcat ttgcgtcatc tttagtagat 240
cctgaggttg accagcagcc catggggcct gaagggaaat gaggcagctg ctgtgtcccc 300
acggaaacaa ccatctgggg actgctggga aatgctgtga atgcggaggg aagtgatgtt 360
tgggttctgt agctgagaga tttttattca tttttaactg ccccccaacc ccactccaac 420
tccttctcca ccacccattc tcccaatggt ctttagaaat agattttcat ctgatattct 480
gcagaaatat caatgagact tggtatggga caggggcaga aaacactaca taggcctcca 540
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ttagtgaccc caatcctata cccaaatcta tgatattctg ggacctcagt gattttggtc 660
ccctcccact tctctagttc gtcatcctcc cttcccatat ccttcaaaag aaccacacta 720
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tagggacatt gtgtacctca gttgtgtcac atgtgagcaa gcccaggttg accttgtgat 1320
gtgaattgat ctgatcagac tgtattaaaa atgttagtac attaaaaaaa aaaaaaaaaa 1380
aaaaaaaaaa 1390

<210> 77
<211> 782
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (29)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (34)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (738)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (748)
<223> n equals a,t,g, or c

<400> 77
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agacctaagg gcacaaatgc agaattcatg accttgtagt tgtggcaggg tctaggaagt 120
cctctctccc caagtagaaa atattctctt gccattcctg aaattccaca ttcatataat 180

ggctgtgcaa tacatgcttc tcaataagaa aattaactgc atgtttactg tgtgctgatc 240
acatcagatt tttatgttta aaaaaatctc attatggatt gagtccagcc cagctctaag 300
agaaaaagaa ggcccatatg ggagacttca stctcattat tattgccttt atccagcagt 360
gcttatgaag ccccctaccc tgtcccattc cagaaaccat aagactcagg cagttcttga 420
ttctggaggc ctgcctggta agataagata gtataatttg gaactgagaa cataccagaa 480
acagcagaac gagggccaga gcagaaaaat gaaaataagt ggagacactt atggatacat 540
tggtgcaaaa aaagccacgg agcccatact gggcttgata tgactttgag gggacagcag 600
attaatactt aatgagggtt aaacctgacc agtctttcta cagtgacagg ccacactgca 660
tgaatgggga gaaccaatga atccattgtc ctctgcctat tttcctgtgc acagtcacat 720
tccctcctta agaatctncc ccttccancc tttacattaa ccaagggaca ctgaatcttt 780
ca 782

<210> 78
<211> 278
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (8)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (27)
<223> n equals a,t,g, or c

<400> 78
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tgctgctcct tttgctgctg tcccatgtgc tcctgagaat gagaaccctg cctttgcaac 120
aaaccatgcc ccggtaaatg caaaaccaca tgctctgtgc cccgagagaa aacctctaac 180
cagcaaggaa aatgtattga tgcattcctc cattttggca cctgraagag agtcttggrg 240
aactgcagga gagggggaaa actggaaaaa aaaaaaag 278

<210> 79
<211> 828
<212> DNA
<213> Homo sapiens

<400> 79
gccaatcaat gagcagtata gagaatttct ggaagggaga cacaagaagc tgttagaaag 60
ggcggcttcc agggaagttc tagggagtct gggatgaatg agaaacttat cctaacaact 120
tttgggctct ctgaattttt tttagtatct gcaagtattg tacttgttca aatatgttta 180
aggctgcagg ctgtattcta aactccttga aagtgagaac caggtttcac tcatatttcc 240
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tgaacccagg actatggcct tctgccactg cctgctttcc tcttgctgct ggggcctagg 720
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aacaaagact ttgaagatga gcggggagga tcgcttgagc ccaggagc 828

<210> 80
<211> 342
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (198)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (215)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (319)
<223> n equals a,t,g, or c

<400> 80
caagttggga agaactgata tcttacggat actgttaaag agaactaaat atggcctgag 60
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tagacaatat tgaaaaccta acctagaagt atgcacctgt aacaatagct aggtcttggc 180
caatgcctgt ggccatantt cagccattca tacantgctg agtgttcaaa gtctgttcaa 240
ataagggaaa caacgaggtg taaccaatcc agctgttctt taccttactt ccaaattctg 300
tacgtcattt cccattttnt gtctataaac cttcttccac ca 342

<210> 81
<211> 537
<212> DNA
<213> Homo sapiens

<400> 81
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gctcaccggt acaccagggg ttggaaaaac cacactaggc aaagaacttg cgtcaaaatc 120
aggactgaaa tacattaatg tgggtgattt agctcgagaa gagcaattgt atgatggcta 180
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ccaaatgaga gaaggtggag ttattgttga ttaccatggt tgtgatttct tccctgaacg 300
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aacaaggggt tataatgaga agaaactaac agacaatatt cagtgtgaga tttttcaagt 420
tctttatgaa gaagccacag catcctacaa ggaagaaatc gtgcatcagc tgcccagtaa 480
taaaccagaa gagctagaaa ataatgtaga tcagatcttg aaatggattg agcagtt 537

<210> 82
<211> 292
<212> DNA

<213> Homo sapiens

<400> 82
tggacagaaa attcaatcct ttattttttt ctctgtaaat gcacgggcta tgagatagca 60
acaaaaaatg catagttaat ggtcatagac tttattccaa aacataattg gaaaatagaa 120
wctgagccat tgccaaatgg taaagaaatg aaaagttttc acagtgacta ctgaatatac 180
caagagcttt tggcagtact gctggctttc tgggtgatta attaggtaaa cttggaatat 240
tcccagtaaa agtttgagaa tgcataaaat tataccattt tgaaaaatat aa 292

<210> 83
<211> 352
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (291)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (345)
<223> n equals a,t,g, or c

<400> 83
ggcacgagtk aaacttgctg ttttgttcct gtgtcttgtc tttggttggt atttcagtaa 60
gtttttggta ttctcaaatt ttatctaaat ggataaacta ttaacataga acataaaccc 120
caattctcca tttcattttt ctcttaggca tgaatcatac aaaactcaat atagagcaat 180
gtttgtaatg aattgttcta ttaacaaaga ggaggttcta agatrtaaag cctcagagga 240
acaggaagga aaaggcgggt ccataaggaa gatgaggtct taaccgggga ngatgctgct 300
tgaggagggc cagagacagt tgtgggagga aatcttttca ccccnttcat gt 352

<210> 84
<211> 404
<212> DNA
<213> Homo sapiens

<400> 84
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cttttcaaat ataaagcagc taaagttaac taaaccacta gcaatgtttg aaaacagaac 180
tctaaaactt ttttttaca tttatatagt ttgttcttaa cactaaaaaa aaaaaagttc 240
acatttcaag ttataaactt acctcagtag tgtacatgaa atggttttga aacaatagga 300
acagataagt cccagatagg rggctcactg atacttaatt ggccatgtca ccaatgtttg 360
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<210> 85
<211> 1555
<212> DNA
<213> Homo sapiens

<400> 85
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caagaagcag ccgccaaagt ccttgaggag tatggagctg gagtgtgcag tactcggcag 180
gaaattggaa acctgggaca agcatgaaga actagaggag cttgtagcaa ggttcttagg 240
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tcttgttggc aaaggttgcc tgattctgag tgatgaactg aaccatgcat cactggttct 360
gggagccaga ctgtcaggag cmaccattag aatcttcaaa cacaacaata tgcaaagcct 420
agagaagcta ttgaaagatg ccattgttta tggtcagcct cggacacgaa ggccctggaa 480
gaaaattctc atccttgtgg aaggaatata tagcatggag ggatctattg ttcgtcttcc 540
tgaagtgatt gccctcaaga agaaatacaa ggcatacttg tatctggatg aggctcacag 600
cattggcgcc ctgggcccca caggccgggg tgtggtggag tactttggcc tggatcccga 660
ggatgtggat gttatgatgg gaacgttcac aaagagtttt ggtgcttctg gaggatatat 720
tggaggcaag aaggagctga tagactacct gcgaacacat tctcatagtg cagtgtatgc 780
cacgtcattg tcacctcctg tagtggagca gatcatcacc tccatgaagt gcatcatggg 840
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aaccacactt ctgtggccat ctcacgtgaa agacattgcc tcagctactg aaggtggcca 1380
cctccactct aaatgacatt ttgtaaatag taaaaaactg cttctaatcc ttcctttgct 1440
aaatctcacc tttaaaaacg aaggtgactc actttgcttt ttcagtccat taaaaaaaca 1500
ttttattttg caaccattct acttgtgaaa ccacgccgag ccctatgcag tctca 1555

<210> 86
<211> 455
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (430)
<223> n equals a,t,g, or c

<400> 86
ggcacgagcc agagccgact gcaaatcact gaactgagct ggcagctgct taggggtttg 60
catgatcaag gcgattttta taacctagaa gggcctggac tgtagaagca gattccagct 120
gaggcccagg cactgccttg ctgtggtgag cacggcggct ctgstcttcc ccgccgagct 180
ttctcatcag tgaagtgggg tagtgacagc atgcgagggc acggagctgt cagcaggctc 240
cagagaccat ggccataaag cactgacact gacacggccc cagcaagccc ttkgggaagg 300
gcagccacca cckttgctgc tgytgtcact tactgttgct gttgatttaa ggcaktacat 360
actcaggtyt catagcttgt aaaamaaagg aaaaatgaaa agtcaccatc atcccagcaa 420
aatgtaaggn tcccctgctg cccagattgg aatgt 455

<210> 87
<211> 675
<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (427)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (528)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (564)
<223> n equals a,t,g, or c

<400> 87
ggcacgaggt cgggctcgga ggaggatcca gagacggagt ctgggccgcc tgtggagcgc 60
tgcggggtcc tcagtaagtg gacaaactac attcatgggt ggcaggatcg ttgggtagtt 120
ttgaaaaata atgctctgag ttactacaaa tctgaagatg aaacagagta tggctgcaga 180
ggatccatct gtcttagcaa ggctgtcatc acacctcacg attttkatga atgtcgattt 240
gatattagtg taaatgatag tgtttggtat cttcgtgctc aggatccaga tcatagacag 300
caatggatag atgccattga acagcacaag actgaatctg grtatggatc tgaatccagc 360
ttgcgtcgac atggctcaat ggtgtccctg gtgtctggag caagtggkta ctctgaaaca 420
tccaccnctt cattcaagaa aggccacagt ttacgtgaga agttggctga aatggaaaca 480
tttagagaca tcttatgtag acaagttgac acgctacaga agtacttnga tgcctgtgct 540
gatgctgtct ctaaggatga actncaaagg gataaagtgg tagaagatga tgaagatgac 600
tttcctacaa cgcgttctga tggtgacttc ttgcatagca ccaacgggaa taaagaaaag 660
ttatttccac atgtg 675

<210> 88
<211> 493
<212> DNA
<213> Homo sapiens

<400> 88
gtcgccctag gctgggactc tagtaggtct tcggctcagt tttggctgca gcgcccgcgt 60
agatcgcttc ggccgsgttc tacgcccggc tcaactatga gcckgtgcgc ccaggcggcg 120
gaagtggcgg ccacagtgcc aggtgccggc gtcgggaacg tggggctgcg gccgcccatg 180
gtgccccgtc agcgtccttc ttcccgccgc cggtgccgaa ccccttcgtg cagcagacgc 240
agatcggctc cgcgaggcgg gtccagattg tccttcttgg gattatcttg cttccaattc 300
gtgtcttatt ggttgcgtta atttattact tgcatggcca ttgctgcatt tcaacagtat 360
gctgtcctga aaagctgacc cacccaataa ctggttggag gaggtaagaa atattttgtc 420
caaaatatta ggacataata ttaaattaag atatactaaa tcaatataag aagagttcat 480
catagtttag tca 493

<210> 89
<211> 416
<212> DNA
<213> Homo sapiens

<400> 89
gtggggatgg tgtcgcatag cagccgctgc cgctttggct tgctcgggac catttggctg 60
gacccagagt ccgcgtggaa ccgcgatagg gatctgtcag ggcccgcggc cgggtccagc 120
ttggtggttg cggtagtgag aggcctccgc tggttgccag gcttggtcta gaggtggagc 180
acagtgaaag aattcaagat gccacctawt ataaactgga aagaaataat gaaagttgac 240
ccagatgacc tgccccgtca agaagaactg gcagataatt tttgatttcc ttatccaagg 300
tggaagtaar tgagctaaaa agtgaaaagc aagaaaatgt gatacacctt ttcagaatta 360
ctcagtccac taatgaagat gaaagctcaa gaagtggagc tggctttgga agaagt 416

<210> 90
<211> 1467
<212> DNA
<213> Homo sapiens

<400> 90
ggcacgagtt catcttcatc ttctcagctt gctccaaatg gtgcaaaatg cattccagta 60
cgagaccgtg gcttcctggt gcagacaatt gagtttgctg aacagcggat ccctgtatta 120
aatgaatatt gtgtggtttg tgatgagcca catgtgtttc aaaatggccc tatgcttagg 180
cctaccgtat gtgaacggga gctgtgtgtg tttgcttttc aaaccctggg agtaatgaat 240
gaagctgctg atgaaatagc aactggagct caggtggtag atctactagt atccatgtgt 300
aggtctgcgt tggaatctcc tagaaaagtt gtgattttcg agccatatcc ttctgtggta 360
gatcctaatg atcctcagat gttggccttc aaccccagga aaaagaacta tgatcgagta 420
atgaaagcac tggatagcat aacttctatc agagaaatga cacaagcacc atatctggaa 480
atcaagaagc aaatggataa acaggacccc cttgctcatc ccttactgca atgggttata 540
tcaagtaata gatcacatat tgtgaaactg ccagttaaca ggcaattgaa gtttatgcat 600
actccacatc agttccttct tctcagcagt ccaccagcca aagaatccaa ttttagagct 660
gctaaaaaac tctttggaag cacctttgca tttcatggct cacacattga aaactggcac 720
tccatcctga ggaatggtct ggttgttgct tctaatacac gattgcagct ccatggtgca 780
atgtatggaa gtggaatcta tcttagtcca atgtcaagca tatcatttgg ttactcaggg 840
atgaacaaga aacagaaggt gtcagccaag gacgagccag cttcaagcag taaaagcagc 900
aatacatcac agtcacagaa aaaaggacag caatcccaat tcctgcaaag ccgtaactta 960
aaatgcatag ccttatgtga agtgatcacc tcatctgacc tgcacaaaca tggagagata 1020
tgggttgtcc ccaatactga ccatgtctgc acacgattct tttcgtcta tgaagacggc 1080
caagtgggag atgcaaatat taatacacaa gaaggaggca ttcacaaaga gatcctccga 1140
gtaattggta atcaaactgc tactggttaa aggaccacca tttaattaac atgattcgaa 1200
agccttcctc gggttcaaag ctggattttg aactgaagaa gattataaaa ttatttattg 1260
ttattataaa caaaattaac cctttgaata ctgatttttt ttcttagtat ttctaagtat 1320
ctcattaaat acctaaaatg gtataagatt tatcaattgt agggttatgg aatctagtaa 1380
taaaatttca acagcactta aactgaagtt tgggttgctc atacaataaa cagattgaaa 1440
aaacaaaaaa aaaaaaaaaa aaaaaaa 1467

<210> 91
<211> 1793
<212> DNA
<213> Homo sapiens

<400> 91
ccacgcgtcc gatttgtccc tattgttcta tttttaaata aatatacaat cattgttttg 60
cattgaaatg catatttgta cattttattt gataatatta ttttgggaaa ttgtaatctg 120
ttgttttgtt tgtttgttaa gggaagcacg aagaagaatt tacaaatgtg aataaaattg 180

tttaagatta ccaatagttt cttttctgga cttgaaatag ttacgtttct aaatatgaga 240
aaaataactt tgcctaaaat ttcagtataa tgaccaggtc ttctctccat tttagagaag 300
cagtccaatg tggaacagat aagacggcag cgatccagtg aggtcaattc cccacagagg 360
aaagctatgc atacctaact taatggaagg taaacttctc ttcaattaat gatgtcctcc 420
ttttctcaag gtgtccaaag acaggaggtg gtctgtaaaa ggttggatga caactccatt 480
gtccagaaca attactgtga tcctgacagt aagccacctg aaaatcaaag agcctgcaac 540
actgagccct gcccacctga gtggttcatt ggggattggt tggaatgcag caagacttgt 600
gatggtggga tgcgcacaag ggcagtgctc tgcatcagga agatcggacc ttctgaggag 660
gagacgctgg actacagtgg ttgtttaaca caccggcctg tcgaaaaaga gccctgcaac 720
aaccagtcat gtccaccaca gtgggtggct ttggactggt ctgagtgtac tccaaaatgt 780
ggtccaggat tcaagcatcg gattgttctg tgcaagagca gtgacctttc taagacattc 840
ccagctgcac aatgtccaga ggaaagcaaa cctcctgtcc gcatccgctg cagtttgggc 900
cgctgccctc ctcctcgctg ggtcacagga gactggggcc agtgttctgc tcagtgtggc 960
cttggacagc accttggctg atgctggaag aggagggcag tcagtgtcac ttctgggatg 1020
tgccccagca ctgagaacaa aatgcaggca tcccccgggg cagcatcaga gtgcctttct 1080
agagggagcc acgcacagaa tgtaacagga tgaaacagtt tcaagtaagc cttgaattga 1140
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aaccccaggg aaactggtac cctacacctg ggagcagtat ctgccactgg gataaagtcc 1380
tactaaaaaa ggaacggtaa atgtacccta atgattaaac cccgtgagat acatatgatt 1440
tccaaatagt ccatttcatt aggaactttt ttgtttgaat gaatgtcaca taggtatcct 1500
cagtaacaca gaacgaaatt acctttgtat tattgtgatt agttgttgct tattatttta 1560
tactcagtaa taatgtggta cactgttaat ttttttgctt ttgtaaatta tattctaatt 1620
tattgccatg tttcctaaca cttgtcctac attcattctc ctgcttgtaa tgaaaatgaa 1680
aaaatcattg taacacttga tggagtgaaa ttccacgcca ggcacagaat tttttgaca 1740
tagataattt agtaaaataa aaattcagct tataataaaa aaaaaaaaaa aaa 1793

<210> 92
<211> 538
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (24)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (53)
<223> n equals a,t,g, or c

<400> 92
gcccaaggat tccggcacga gganttkttg ttggttgggg gccttttggc sgntgacgga 60
gactgcccag gtgtggtcac catgttcctc tccgcggtct tctttgccaa gagcaagtca 120
aaaaacattc tggtgagaat ggtgagcgaa gctgggacag gtttctgctt caacaccaag 180
agaaaccgac tgcgggaaaa actgactctt ttgcattatg atccagttgt gaaacaaaga 240
gtcctcttcg tggaaaagaa aaaaatacgc tccctttaaa cggtggattg aaaatgactt 300
tgatttataa agagaagact gagggcgggg atactgattc agaaatcctg tagcgtgtaa 360
taaaagaaga ggaaatggca tggaatcact gcctcctgtg atttgaaggc cattgtgaag 420

gaaaacaatg cagtgaaaga aagttcttca tattaggaca gatatcattg catcacattt 480
atttatcttt ctgggtattt ttatagccct taataaaaaa tattaaaatw gwaaaaaa 538

<210> 93
<211> 483
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (444)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (483)
<223> n equals a,t,g, or c

<400> 93
gggaatctat cataactagt ctagagattt ctcaccaagg gaaattttcc ttatctaaaa 60
gaggaacttc aggtctcaac cctgccagtc acacccaatt aatgtccttc acaaaaataa 120
acagcatatg ttccctttca atttgagttc agtgagctca cagcaaaatt taccttttaa 180
ttttcttcag caaatccaag acgaatatac aaaggatgag attagataaa gatttcagtt 240
tcccgtatgc caccgctggc cgccaatttt ccaaaaaagc ctggctcctc ttttcctgtt 300
cctccatcca agccccccaaa gatctctaac cagaawtaaa caggaagact cagtgattta 360
caaaagacat tttagtttta cacgtacaga aaattctacc cagcattaca gaaattctta 420
gacttcttaa aattcccgga tttnccctgg tatttaacat ttggataagg gagccatggg 480
ttn 483

<210> 94
<211> 719
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (619)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (633)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (643)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (646)
<223> n equals a,t,g, or c

<400> 94
ngggaattgc tgagatgaca gtgtcccaca cagcttcaaa taaaatccat ggaaagatgt 60
tgcatttgtg gaataagtgc ttacttgaaa agcatgttct tcttttattt tcttactgtt 120
aagaattttt atttgtagga tgtttgtttt aatttaattt ttttaaggga tgggggccat 180
catgtggaaa ccagaaaatg gggaaagtgt gaactatcca gacaaagatt cattttgtgt 240
ctatatttgt ttttaattgg cctcatttca aatgtattaa acagttccat acctggattg 300
ggtgtttgta atggttacca aaaaacaaac aaaaaaagaa agaaaaagga aaaaaaaaaa 360
gaaaataatt gtgacatgct tttatcacta ctttattttt caaataacat gtaaatattg 420
taatccattg gattttgttt tgctaacctg ttaataaaaa tatgggacca ttatcctttt 480
aacaaggcta gaatgtcatt tttttctttt tcaacatata cctgatattt tgtggccgca 540
cattttggrt gcattattat aattckgttg actgtaatga catagaatta cacattttkt 600
gktggttaat tatacagang acattttttt canagcttga ganaanaaaa taaatagcaa 660
aatgataacc tattgactcc agtaatcagt gtttcccaat acttcataag aaataggga 719

<210> 95
<211> 613
<212> DNA
<213> Homo sapiens

<400> 95
tattcagcta ctatacagaa aaaggatgaa caaattaatt tatttctaat tgagccagtt 60
agacataatg catataacgt gatatttggt tcatgaaaga gttgttttca tgtggttatt 120
gtagggagta tatataattg tggaaggggt atgggaagag ttgtgtatag ttagttgtta 180
tctctacaag tttgaaagtt ttcccatcaa acattatcaa tataccaatg ttttaaaaat 240
tgagtgaggg ttattatttg tatttgatga aagaaaatcc aaataaagcc cacctagaaa 300
tagatatttt attatatatg tgctatagat atacctatat agtacaaata gacatgtgtg 360
atgcatatat acaatgttat atatgtgtat atgtctgtat acacactgag tctgtaatat 420
gtatacacta aatttgtgky amgctaacak cttcagggtc tgcactgtga actcccckgg 480
agataagtaa gtccacttta gaataaagag ttcttttgag acttcagtta ctaacgtgct 540
ttaagaggta tctactttat aactgaattc tatgtcgttc atacgtagag ttacagtaag 600
ggtctagtat gtc 613

<210> 96
<211> 816
<212> DNA
<213> Homo sapiens

<400> 96
gggaaaggag ggtcaggcga gtccacgagg aggttcgagt gaagatcaaa gacttgaatg 60
aacacattgt ttgctgccta tgcgccggct acttcgtgga tgccaccacc atcacagagt 120
gtcttcatac tttctgcaag agttgtattg tgaagtacct ccaaactagc aagtactgcc 180
ccatgtgcaa cattaagatc cacgagacac agccactgct caacctcaaa ctggaccggg 240
tcatgcagga catcgtgtat aagctggtgc ctggcttgca agacagtgaa gagaaacgga 300

ttcgggaatt ctaccagtcc cgaggtttgg accgggtcac ccagcccact ggggaagagc 360
cagcactgag caacctcggc ctccccttca gcagctttga ccactctaaa gcccactact 420
atcgctatga tgagcagttg aacctgtgcc tggagcggct gagttctggc aaagacaaga 480
ataaaagcgt cctgcagaac aagtatgtcc gatgttctgt tagagctgag gtacgccatc 540
tccggagggt cctgtgtcac cgcttgatgc taaaccctca gcatgtgcag ctcctttttg 600
acaatgaagt tctccctgat cacatgacaa tgaagcagat atggctctcc cgctggttcg 660
gcaagccatc ccctttgctt ttacaataca gtgtgaaaga gaagaggagg ttagccaagc 720
ccccacccca tcccactccc cttccctcmc cagatattta tgtgaaatga actgcagctt 780
tattttttga aataaaaact tttaaaaagc aaaaaa 816

<210> 97
<211> 577
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (38)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (575)
<223> n equals a,t,g, or c

<400> 97
cagaagccaa aaaggtctta aaattggaaa tagatgtntt tattgtactt cagccaacag 60
caagccaggg gaaggaacat acataaatat gacaggtcat atatgaaatt tggctctcct 120
cctatcaaag tagcctagga gcttggagga agcctaatta actaaaacag gaaaaaagca 180
tactcatctg atgtaaaaac tcatcagctg taaattacca acattaaacc agaagtcatt 240
accagttaaa atgtgtggtt ttcatcttat tcttaaatag gagaggtggr cagtagtgta 300
agtaacattg ctttaaagrc ataaagcttk tcctggtaaa catggtctaa atgagaaatg 360
cctccatctt ttcaggtaga accagatttc aggcatagct cagctacatc tgtatttgaa 420
atacaataaa aatatttctt atgtctctgt attctctttt aaaaagaact gctgactggc 480
tcctgtctct tcagtaacac tgattttttt ttaaagaagt gatatgttgg actctgttgg 540
agaagaatga gcactagtat tcagccacaa gtgcnat 577

<210> 98
<211> 484
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (456)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (476)
<223> n equals a,t,g, or c

<400> 98
cttgcagtcc acttgctgaa gaagttgtgt catttctctg gaagaatttc caaaattctg 60
gatttttttt tttttttgga gtatttcatc agctgaaaag tgattctyac tttgagtttt 120
cttcctatat ttgtatagtg agttcctttt tccttcctct ttatccctcc tgttttactt 180
tatacctctc tattccttgc tcaaattatt gcaaaagcct ctatagaaag tcctctgtga 240
tctgactcct gcagactctt ccagattttt ctgcccaagg cctttactga gctcaggact 300
ccagctaaat caaratackc atgttctcac ccagagtgac aaaatcctgc agataggttt 360
aagacctagt gggmtcagag cagtagctac tgggaagtta aaaggaaggg gttagaaaat 420
gaatgggaca aaggcacact tctgatggag atgaancact tgaaagtgag tggtgncttt 480
ggag 484

<210> 99
<211> 441
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (328)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (331)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (332)
<223> n equals a,t,g, or c

<400> 99
aattcggcac agggaaaaag gctgagcgga gagccgtgct gcctggcccc tcctcaccgc 60
ccttccccgc acctcttggc tgtaccggga gcctctgaag caccggaaat gaagggtttt 120
ccaggcctgg ctcttcacts catccttcag gggaactttg aagccatgga gacatctggc 180
tttggagcca tggcgattcc cctgccactc tccttgctgg gataaagcca gggcgtggca 240
tcctgggatg atgttccctg ctgctgagtg tgcacacaac ctgagctcat cctgtgtacg 300
tcagctacac atgctcgcat ctaatttncc nnaacaacct agccagtact attgcttctc 360
ctcctcttac agatggggag atgatgacat atagaggtta acttatcaga gaccacacaa 420
aaaaaaaaaa aaaaaactcg a 441

<210> 100
<211> 524
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (510)
<223> n equals a,t,g, or c

<400> 100
aaagaaaacg aaaaagaaag cccaaggcaa agaaggggga aggaaaacaa acttcgccac 60
tctytcttct ccttcctaac cctttgtyta gagcaccaca ccgctcacaa actctttcca 120
aatgctcagt tggctcccaa agttggagcc tggcatgggc akggagccca caaaactcta 180
accaaactgg akgctggcat gggagaartg cttctggttc actcttccta ccctctccct 240
cctaaccctc tccttgcctg acagggagcc cctgtggcct ggactctagg ggatgccgcc 300
accagaaacc cctctgccaa tccctamctt gcaccctggg aaytgcagta acttattctc 360
aaaggcttta aacacagaga tcctctcagc ggccgtgggc ctgccccttg tcctarccct 420
tgccacgttg agggtccaac ctccaaggga caggcactgc cccaccaacg gcaaatccaa 480
aattctttca aaaaaaaaaa actgaaaacn caacccaaaa aagc 524

<210> 101
<211> 614
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (355)
<223> n equals a,t,g, or c

<400> 101
ggagaaggtt tctctctcat ctccttctcc agcaaccttg gccatggacc agccggctgg 60
cctgcaggtg gactacgtct tccggggtgt ggagcatgcc gtgcgggtga tggtttctgg 120
gcaggtgctg gagctggarg tggaggaccg gatgacggct gaccagtggc ggggcgagtt 180
cgatgctggc ttcattgaag atttgactca caagacaggg aacttcaaac agttcaacat 240
cttctgtcat atgctggagt cagccctcac tcagagtagt gagtcagtca ccctggacct 300
gctgacctac acagacctgg agtccctgcg gaaccgaaga tgggggggcg ccagntcctt 360
ggccccccagg tcggcccagc tcaactccaa gcgctacctg atcctcatct actccgtgga 420
gtttgacagg attcactacc cgctgcccct cccgtaccag ggcaagccag accccgtggt 480
tctgcagggc atcatccggt cactgaagga ggaactgggc cgcctgccca gtccctgccc 540
tggccccgtc cctcctgctg cccctggggg tctcaggtgt gtgaggccct gaccctgccc 600
tctccccagg cagt 614

<210> 102
<211> 544
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (2)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (5)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (6)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (10)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (12)
<223> n equals a,t,g, or c

<400> 102
cnaanntgan anaaccctca ctaaagggaa caaaagctgg agctccaccg cggtggcggc 60
cgctctagaa ctagtggatc ccccgggctg caggaattcg gcacgagaga aaaattattt 120
gtatataact ttaaaaggag tagaagggct ttttgcagag ttattacgtt tgaagtatac 180
tttatttctt gaaaaaatta cagatttttt gtaaataatg atgtaattca actctcaaaa 240
tatttcctac tgtttcttta ttccagttgt attcacatgt gaaagcatgt gatcagttat 300
tgctgcatta aaaacatgag tctttttat taggtggcca ttatttatga tcttttctat 360
gaaagagtaa ggacattaaa atgtaagatg catgatgaaa aattaagtga agaggctctt 420
tatggttaat ttatattgaa taatgcatta ggtaggtgtt cagagtaata ttttgcgttg 480
tgagaacatt tttaatttta tttaaaatta aatgaaaata aattagtata ttattgtact 540
aatt 544

<210> 103
<211> 1887
<212> DNA
<213> Homo sapiens

<400> 103
ggcacgagag gaaggaactg gtttcgggga gccctgggcg gggcggctgt ggggaggaag 60
gtgacgtgca ggggaccaga ggctctgcac tgctcctagg acagctcatc tgtaatcaga 120
aaaaaaataa ataaaataca gaacgctgac tcctccgtga gacagatcgg ggaccttagc 180
actttaatcc ctcccttctg agcgctcggt gtgcactttt agactatagc tgtttcattg 240
acgtgtcact ctccatccag tgtccttgat gtggctttta gagacttagc agaaaattcg 300
acacaagcag gaacttgatt ttttaagaaa aaatattaca ttttgaggac attttgacaa 360
gtaggggaag agagggcttc tgttgttttg ttttgttttg ttaactaaac ctgaagtatt 420
aattccacaa agacactgtc cctcaggacc actcaggtac agctctgcca gggacagagt 480
ctgctagtgg gaggtctcag gtggggcggt gtgttctgtg ccatgaggca gcgacaggtc 540
cagatggatg tcgtcaccac cttcctcagc tctcatcacc tggtcgtacg ccaggcccac 600
ctcttcccag caagggacgc caaagaactg cagtttttat tctgagtctt aatttaactt 660
ttcatcatct tttcctattt tgragaattt tttgtaatta aaagcaatta ttttaaaatg 720
tgcaagccag tatctcacaa ggcatggatt tctgtggaat ttatttttat tcaaataacc 780
atatttatct ccaggctgtg gaatcgccac tttctttgtg aagacagtgt ctctccttgt 840
aatctcacac aggtacactg aggaggggac ggctccgtct tcacattgtg cacagatctg 900
aggatgggat tagcgastgt gggagactgc acatccggac ctgcccatgt ctcaaaacaa 960
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agacttgctc aaaagattcc tttttatcat ccccacgctg tgtaagtgga aagggcattg 1140

tgttccgtgt gtgtccagtt tacagcgtct ctgcccccta gcgtgttttg tgacaatctc 1200
cctgggtgag gagtgggtgc acccagcccc gaggccagtg gttgctcggg gccttccgtg 1260
tgagttctag tgttcacttg atgccgggga atagaattag agaaaactct gacctgccgg 1320
gttccaggga ctgktggagg tggatggcag gtccgactcg accatgactt agttgtaagg 1380
gtgtgtcggc ttttycagtc tcatgtgaaa atcctcctgt ctctggcagc actgtctgca 1440
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cagcataagc tgatggtatg taaggaaccg atgggccatt aaacatgaac tgaacggtta 1560
aaagcacagt ctatggaacg ctaatggagt cagcccctaa agctgtttgc tttttcaggc 1620
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ggctgagaaa catgttgctg agatgcaatc ctcagtgttc tctgtatgta aatctgtgta 1740
tacaccacac gttacaactg catgagcttc ctctcgcaca agaccagctg gaactgagca 1800
tgagacgctg tcaaatacag acaaaggatt tgagatgttc tcaataaaaa gaaaatgttt 1860
cactaaaaaa aaaaaaaaaa aactcga 1887

<210> 104
<211> 253
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (226)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (228)
<223> n equals a,t,g, or c

<400> 104
agattttgaa cttaaattat attctatatg tgtatcttcc taggcaaaag ctgtaatttc 60
cagagagacc attaggaaca ggtagtatct attttyctcc attatttatt tctagaaact 120
cataaaatgg attgtatttt tctataagaa caaaatatta attaaggtat agatgactga 180
ccaagggstt aatcaaataa aatgactaac agcatctatc cataangnca cacaagcctt 240
atgttctcat ctt 253

<210> 105
<211> 705
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (671)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (688)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (698)
<223> n equals a,t,g, or c

<400> 105
cccaatctct agctagtgtt gcttatcaaa taaatgcatt ggccaacaat gtactccagt 60
tgctggatat ccaagcctct cagcttcgga gaatggagtc ttccatcaat catatctcac 120
agactgtgga tattcataag gagaaagtgg cacgaagaga gattggtatt ttgacaacaa 180
ataagaatac atcaagaact cacaaaataa tagcacctgc gaatatggag cgccctgtaa 240
gtatattcgg aaacctatcg attacacagt tctggatgat gtgggccatg gtgtcaagtg 300
gctaaaagcc aagcatggaa ataaccagcc tgcaagaact ggcacactgt cgagaacaaa 360
tcctcctact cagaaaccgc caagtcctcc catgtcaggc cggggaacac tgggacggaa 420
tactccttat aaaaccctgg aacctgttaa acccccaaca gttcctaatg actatatgac 480
cagtcctgct aggcttggaa gtcagcatag tccaggcagg acagcatctt taaatcagag 540
accaaggaca cacagtggaa gtagtggagg aagtgggaag ttcgaggaaa acagtggtag 600
cagtagtwtt ggcwttcccw ttgctgtgcc tacaccttcg gcacccayta ttttgaaacc 660
atttgttgat ngttccaatt tccaccgnca ccactttnca ccaaa 705

<210> 106
<211> 920
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (920)
<223> n equals a,t,g, or c

<400> 106
gctagaagtg gattggagcc tctttgatgg atttgcagat gggttaggag tggctgaagc 60
catttcctat gtggaccctc agttcctcac ctacatggca cttgaagaac gcctggccca 120
ggcaatggaa actgcccttg cgcacttgga gtctctcgca gtggatgtag aggtggccaa 180
tccaccagca agcaaggaga gcattgacgc tcttcccgag atcctggtca ctgaagatca 240
tggcgcagtt ggtcaggaga tgtgctgccc catctgctgt agcgaatatg tgaaggggga 300
ggtggcaact gagctgccgt gccaccacta tttccacaag ccgtgtgtgt ccatctggct 360
tcagaagtca ggcacctgcc ccgtgtgccg ctgcatgttc cctcccccac tctaaagacc 420
aaggccgttt actcctggtc tgattatttt ccccatctga aatccacaat actgcaggag 480
ccctcttgaa attaacaatg gaaataaaac caatcagtca gttagcctaa acctattgat 540
tcctcgtgat tatttccaat gtgaaaacag ttgtgtatga ttgcattaaa aatcatatca 600
tcttttagag gttagaaaag ggaaaactaa actttctaaa tgctacttga gattgcagta 660
agaagatacg ttttctaacc tgaaagttaa atcgcatttg ttttcttcag tagaatggga 720
atgtgttgct gttacttgta atgtcaagtt tatctgttaa atatgtccaa aaggcaaaat 780
catttttgtt gcatgttatg ggtcgatgtt cctgtaattg cagtgccgta aaagcttatt 840
aaagttgttc ttttggtttt aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 900
accccggggg ggggccgggn 920

<210> 107
<211> 466
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (7)
<223> n equals a,t,g, or c

<400> 107
nggcccntac tcgggcgctc ccagarggag ccacctctca gtgcctcamc tccccctgcc 60
tcccagcctc cgcagatgag gttcctgccc cttcctcctc gtaaccaaaa ccctcactgc 120
tcccaggacg gtcttattta taaaccagat acatgttctt agtctggtcc cagaccaagg 180
agctggtcag acggcccttt ctaatcctac atgttgagct tatgtaaaaa atgttgtttc 240
ctcctgtttt tggttccttt cttacccaca aaccattact acttgaaact taaaaaactc 300
gccaagtgta aaggctaaag agaagcagtt tgacggacct tgtgatttgt actgtttgct 360
gcggagctat ttaaagattt tggaataaat atacaaaact acggttgtga aataaaaact 420
taaattgtat attttgaaaa ataaaacact gaaaagaaac aaaaaa 466

<210> 108
<211> 323
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (111)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (113)
<223> n equals a,t,g, or c

<400> 108
actatttttt tattttataa atctttgtag aaataagcaa tgaaatacta ctttcatctt 60
ttgaaatggg atttttcaag gcagtgtcct tttggcatta aggtaggggg ncngttaata 120
ttctctctgc cttgtttcca cgtggaatca atattaaagt catggacatt ttaaaatctc 180
aatttaattt cttcttattt actatgcagt atagccgtgg aacaagtaat gtagatttag 240
ttttctcatc ttcaaatgcc ctgatcaccc tacctcacag ggttgttgtg gggrtwaata 300
aaactttatg gragcaaaaa aaa 323

<210> 109
<211> 448
<212> DNA
<213> Homo sapiens

<400> 109
tttttttcaca gcatattaga aatgtttatt aagaataatg gcatgaactg cttttaacaa 60

tttagaaaag acccattccc cccgcccscc cccgccccca gatccagggc acttcctcta 120
agtaaayaca aatatttctg tagtgaactg tatgcatatt cccactgagt aaaggttata 180
agaagcctca ggtcaggtct taccaccaaa cttgaaaaca cttggaatgc agctgggcag 240
ggacttgagc aggttttgtc ttgataagca ggtaagaatg gcagaacact ggcttattgt 300
caaccaatgt ttttttatat acctgaagta ttcacagcaa cttattttaa gaagcttttt 360
aaaagttcta cacctccacc cccacaactc cccaatccag aacatggaac aagggtgtgg 420
agccgtttga tggacttggg tctgttcg 448

<210> 110
<211> 849
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (32)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (33)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (39)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (841)
<223> n equals a,t,g, or c

<400> 110
ggtgactccg tctcaaaaaa aaaaaagaag gnngtaccna cagtatacgt gtgggcactt 60
gtgcttgagc ctgtattaaa ggaatcaggc caggcacagt ggctcacgcc tgtaatctca 120
gcacattggg aggctgaggt gggcggatca cctgaggtca ggagttcaag accagcctgg 180
ccaacatggt gaaaccccat ctctactaaa aatacaaaaa ttagctaggc ggggtagtgc 240
atgcctgtaa tcccagctac tcaggaggct gaggccggag aatcgcttga gcccgagagg 300
tggagactgc agtaagccaa gatcatgcca ctgcactcca gcctgggcaa cacagggaga 360
ctccatctca aaaaaaaaaa aaaaaaaaaa aagacattca acttgaggct cctgttagtt 420
aagctatctt ctttcacttg aagcaggttt gagaggccta ggccagaatt taaattcctt 480
ttatgaatag atttcccttt cttcctgacc ccaaggtcag aggagactat atattccatg 540
gctgcctcta agactaggaa taggaatatc tgaaaacagc atttctaagg gtggtaacca 600
caggtcgatt ttaatacgag tcctttttct tgtagaggta agtaaaatct tcctgacaag 660
gtagtcctct tttcacggca cagacaatgg gctttctgtt tatgaggggt gagaagtgat 720
gtttgttact atgttctcca gcaagtaaac attcctctgc tcacctccca acaagactaa 780
cagtcttttt agaagtaaat atattcaaga caaacgagaa aatcctggct acccaagtcg 840
ngtatatac 849

<210> 111

<211> 876
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (871)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (876)
<223> n equals a,t,g, or c

<400> 111
aaaaaaaatt tacaaaaaaa caamcacama aaaawtatct tttttaggcc agagttttct 60
acaggtatta atgaatattt ttcttaatcc ttataagttt tatgtgttta atatttctta 120
ataccggtag cattaattta tacttttgta gcaacacaat atttttataa acagccggtg 180
cttggctcaa gtcttcacga ggggtttagg cagggccatc ttggggaccc tgtgtaccat 240
gtactgtatt taaaaaaaaa aaaagttacc tattgtcaca cttgctgtgt taattaacaa 300
aagatgttgt gtgcggtctc ctgtatcggt gtggatccaa cagctctcca gggagtcaca 360
ttgcatgggg gttgagttga cggttcttgt gatatgtaaa cccccgagac caaacttgag 420
ggtttattta gggttttctg tttgtccttt gggtttttgt ttcactttgt tttggtgccg 480
tttctccatt tacagccaaa tcagtttcat gatgttcaaa acatttactg atgtcaaatg 540
gaggaaagga acagaaaaaa agatttttac aaagtaataa aatttaaaac tgagctgttt 600
aatgttgctg tttttacctg tctgttcttg tccaaaagtg gaacattccc agggagaaga 660
ggaaggttcc actcggttct ttaagtcgcc aaaagcccca gcccgggatt cagtacctcc 720
cctgcccccc gaattcttgc agcactattt cccagttggt tgatgccaag gcaaaaagat 780
aacttttaac agttagagag gatcagttgc ttaaatgatt tcatgtcagt gttgtattta 840
tggttttaca ataaaacaac ctttaggaaa naaaan 876

<210> 112
<211> 382
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (100)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (105)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (341)
<223> n equals a,t,g, or c

<400> 112
gcctcccagg ttcatgccat tctcctgcct cagcctcccg agtagctggg actacaggca 60
cctgccacca cacccggcta ctttttttata tttttagtan agacnggttt catcatgtta 120
gccaggatgg tcttgatctc ctgacctcat gatccgccca ccttggcctc ccaaagtgct 180
gggattatag gcatgagcca ccgtgcccgg ctattttcag ttcttatgct gtgaaccact 240
ttgccttgta gctttttcta tctttccaaa atcctcactc tgttcattgt ttgtctcagg 300
ggaaaatctt cccccaccga gcttgtaaaa aaactttaat nattgggtgg aggataattt 360
aggatgggta tttattggag gt 382

<210> 113
<211> 1070
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (334)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (882)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (961)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1018)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1070)
<223> n equals a,t,g, or c

<400> 113
ggcacgaggg ccgactggac tttgtgagct ccagctgcta cagttgactg agttcaggct 60
ccatgtagct gggatatact acatggttac ccctcacccc tatggagctt ccaaaagaga 120
ccctccctca aagcacagcc ccttctctga gtgcaaataa tggccatcag aggtcagtca 180
caggtgttag gcaggcatct atgaagctgg ggatgatagc actgacttca gtgcttggac 240
gagaaccagg agagagtgtg tagaaaaagc acagccagcc tcccataaaa ggacagaytc 300
ctgtgacaac cttgtcactc tgttcctccc tgantactct ggggaggtgg aggccagtgg 360
gcagttctaa agctcagcag gtttggagcc attgggtgtg gactcctctc ccagtgttcc 420
tcctgggtgt tcacagatgt tattgaaatg cacactggga accctgcaca ggtaaaacta 480
aggytttatt ggcgtgattg ccaaaggtca cacagggtgg tttggyagag ctgggattag 540
aagcccagcc tgtytctytt cagtagtaat ggagtcctgg gaggtttact aggctttagc 600
ctcaatctgt ggcggcaggg tccacagccc tggggagtga cacagtcatg gtccccatga 660

ttggccagga cctgtktgga gagacacagg agacaagacc ctgctcttcc aggccagaag 720
ggaggggagc cccagagctg ggcagtggca tgccccacag cctggccacc tgcttcggct 780
acgcaccatg cagcagctgc acctggctgc ctcgggaaaa ctctgacctc tctgggaagt 840
ggagccagtg gctctgtggg cgtcctttcc tgcagcctgg anagcaaagc ggctttccct 900
gggactgtgt ggctcctgtc ccaactggcc tccccattcc acattcccat tgctggacca 960
ncaccaggac tgggcacagg gcttcctttt gctgattcat ttcccccta actcatcnaa 1020
attgaacccc atctgattcc cacatgctgg ccctgaaacg gtacaaaggn 1070

<210> 114
<211> 371
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (360)
<223> n equals a,t,g, or c

<400> 114
gtctattaga aaacggtcct aagagattct ttggtgtttg gcactttaag gtcatcgttg 60
ggcagaagtt tagcattaat agttgttctg aaacgtgttt tatcaggttt agagcccatg 120
ttgagtcttc ttttcatggg ttttcataat attttaaaac tatttgttta gcgatggttt 180
tgttcgttta agtaaaggtt aatcttgatg atatacataa taatctttct aaaattgtat 240
gctgaccata cttgctgtca gaataatgct aggcatatgc tttttgctaa atatgtatgt 300
acagartatt tggaagttaa gaattgatta gactagtgaa tttaaggagt atttgaagtn 360
gggtgggggg g 371

<210> 115
<211> 581
<212> DNA
<213> Homo sapiens

<400> 115
tttttttttt tttttttttt tttyttgagt attccagcat tatttatttg atcagagtaa 60
aatacacttc ccatcactac aaactgagca caactacagt tgtctacaca ttcatatttt 120
tgacgtgcca acattttgca ttctacatga aacatttggt ttaaacaaaa tcttaagaat 180
tctctatttt gtttcccatc ttccctcctg ttctctccca tcctccaaag atgttttata 240
ttaactgcta tgagatttat ttgccggtca cgtaatacgg aggacagcag ggaacaacac 300
aagatttacc atgcctaggg gatgaatggc aaacccaact ttggctaatg tcattgagaa 360
caacttggga agcgtgasag gaggatatct catggaagtg ggcagtgaac ctacatttcc 420
atttatcaga agcaaacatg ggaaggttac atacatgatg aagtattgga agttaaagac 480
ttaagacaca aaatcactaa tttaaaagra cmtgcmacmt grgtatcaac ttgctatgta 540
gkgtacatgt aaatgaccca aatattcacc tctagcatcc g 581

<210> 116
<211> 705
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature

<222> (681)
<223> n equals a,t,g, or c

<400> 116
atcggacggg cttaacatga aagcctatag gtcattcttg ctctgggatc tacaggcagg 60
gtaggcacag gtgcagccta agaagggaac ctgcttcctc tcccttccaa agacagtgac 120
agctgactga gggcaaagag caggcaccac tcagaacgtg gtgagtacag ctcagctcag 180
cactcagtca gtggtaactt gtgcccagcc ctgtgctagg cgctgacatt aacaggagca 240
accagggccc aattcctggc cttggagctc aaatctttcc tttgattttt gctcctgatc 300
atcaaggccc cagtggcaac catgtggtaa gtggccaacc aagccctacc cagggtcacc 360
caacacactc tgccttgagc ctctcctcag ggtctattcc ttgcgtggat tatgtggccg 420
tagcatgtta cagttcaaac atgtctccac taccctgtta agagcagcct gggaacgtac 480
aggccatcaa gactatttat ttaaatacaa aaaaagggga aaacacacac acggaaaaaa 540
aattgtaagc acttttttg taaaaccaat gtctgttttg ttacatacct ttcatgtcgt 600
gctttgtaaa tgtcttattt gtgtaataaa gttaatgcaa gtaaaaaaaa aaaaaaagat 660
gggcgaagtt atcccttgtg nggtaattag tttgctgcgc gttta 705

<210> 117
<211> 1196
<212> DNA
<213> Homo sapiens

<400> 117
gcgaccgcct cgcgtacccg gcttgcggtc cacgagcgag cacgcccggg gtggcgatgg 60
ggtcgcgccg aggcagcgga ggttctgcgg gcgactggag gttggcagtg ggcgggagaa 120
agaggaaggc aggcgcggct gggcctcggc ctctggcgcc gcggtaccct ttgtctcggc 180
agcctgacgg ccccgccggg ctctccggag aggggaacgg gcggcgaggg tggcgggtcc 240
tgggcgccct gtgctgcggg gccgagaggc gctcgggtcg cggcgggatc ggccggacca 300
gacagggtta atggaagagc ctggccagtc ccgcgcgggg cccccgcagc gacagccttg 360
gccgcgggga ctggagtcct gagggggaga agcctgccgt tctgaaggct cgggacttct 420
gccccaaaga cttcgccgcc gagaactgcg ggtgcactgc ctcagggaag aagttgagaa 480
ttttgccagg tcatctctgc cagggcacag ttcatcactg tgtgtttagt gtgtttcggt 540
gaagctctcc aagtgtgttg aatcagcgtg cctagcctca agggtgcatc gtgaaaactg 600
aaaccaaagg aatgatacag gcctgctttg tgtgtgtctt cccactttaa gcttgttttc 660
agtacaaata ctcttgcttt aaacctgatt ggactgtggc gagcggacat ctgttcaaag 720
gaggggccga gaccacagta cttctgaagg gggcttgata atgtggaaac attttaagtt 780
ttctctccgg actgttttgc tctctcaatt caggcaagtt actgaagtac gttttttatc 840
tagaaaaagg tttgatgtag tctgtaaatg gtccttgtaa agtacattgc catctcagaa 900
ttaaaagatc cactctcatt tattatgcag aagttagtgg tcattctttc ctgtagatag 960
tttatctcat gtaaagaccc acccagcttg gtttaaattt ttttctcact gacgtataac 1020
catcagcttt gatacttcca ttttcaggct cagactttga atttaaggaa actaaagatg 1080
actttatttt cttttctctt ggtttttttt ttccaaaaac aaaaaataaa tccattacat 1140
gttaacataa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaacggacgc gtgggc 1196

<210> 118
<211> 975
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature

<222> (794)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (845)
<223> n equals a,t,g, or c

<400> 118
tgtccctttt tattctagag gcttttcctt taattcagag attagtggag ataataacgt 60
cagtcaaggc taatgtggta catggaactt gctaatggag gttggacatt ctgtttcagt 120
cttacatgga tattgtttca ttggtgttga ggaagaaaaa aattagatac taccatgcat 180
tgggacagca taattctaat attacattga atatggcttt ttaaaaataa gtattaaaaa 240
gccaatcgtt ttctccattt atctatcttt tttgtttgtt tttaatttgg ttgattgata 300
tgcacccagg ccgtcttatt tttacttgtt aaatgtctgt ctaggaagaa ctgtgattgg 360
aaaggaatta attattatac aaataaatct ggtaggatat gagtggagta agtttgcttg 420
aaacagaagt atattttcta ctttgaatca cctcaccaga gtcatctgtc aagaattatg 480
tataacaatt tatctttatt gcctacatac aacatacttt ttctgaatta agataacttc 540
tatttgtgag ttgaacttca ttatctgcca ttttgtggaa tcaaccttac attytttggt 600
ggractagag ctgattgtca ccacaaggtt atatgacaac tctgttctar grcttatacc 660
yattatatag ggktatacct tttttcttat gcctcagctc tgtacctgac aatttatgat 720
tcagtggagc caagctagaa ggaacaaagg tcatctaaca ctgtgatggg gatgaattcc 780
tgagttttac ctgnacaatg aggtggtgcc ccggaattca caacagagta gtgatagagc 840
ataangatgg ctgctccaga tgactcttgg gtttaagtgt acttgtgatt gaacaagatt 900
tttatctatg aagcttgatt ctacaaccaa aataatagaa atgggggggg ggggaatcat 960
gtctgcttat gcttt 975

<210> 119
<211> 331
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (331)
<223> n equals a,t,g, or c

<400> 119
catatattag tgtgctttga agttgactga aagatatact ggatatcata attatataat 60
ttctaaatag atttctttaa atccatgcta tgttttcttt ttcagtcagg tcctacagaa 120
tgactattgc acttggtcta ttgttttaat agtaaatttt gttattaatc tcctatgtgt 180
taaacgtggg taattgtatt atgttaatac atacttaggg aggaaaagca ggtggatgta 240
aatcagtgat tcccaacttc agcagatggw tagcmgtggg agggtatcct tggagctttt 300
tgtaaatatt tccaaaaaag gggggggggg n 331

<210> 120
<211> 233
<212> DNA
<213> Homo sapiens

<400> 120

tcgacccacg cgtccgccca cgcgtccgca aaactgagag ggataggaaa gaaaaactta 60
tccaggaagg aaaattggat cgaacatttc acctctcata ttaagtctgg caatgatgac 120
tatatgtatt cctgcctaaa taaatcatct attaatcatt aaaaaaaaaa aaaaaaaaaa 180
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aagggggggg ggg 233

<210> 121
<211> 2043
<212> DNA
<213> Homo sapiens

<400> 121
ggcacgagca gccctcggcc ccatccctac gaccagccct tccgtcctgc ccaccccggc 60
agcgactggt gttcctgaag acacataaat ccgggagcag ctctgtgctg agcctgcttc 120
accgctatgg ggaccagcac gggctgcgct tcgccctccc tgcccgctac cagtttggct 180
acccaaagct cttccaggcc tctagggtaa aaggctaccg cccacagggt ggaggcaccc 240
agctcccctt ccacatcctc tgtcaccaca tgaggttcaa cctgaaagag gtacttcagg 300
tcatgccttc tgacagcttc tttttttcca ttgtccgaga cccagcggct ctggctcgct 360
ctgccttctc ctactataaa tccacctcat cagccttccg caagtcacca tctttggctg 420
ccttcctggc caatcctcga ggcttctaca ggcctggggc ccgtggggac cactacgctc 480
gcaacttact atggtttgac tttggcctgc cctttccccc agagaagagg gccaagagag 540
ggaatattca tccccccaga gaccccaacc ccccacagct gcaggtcttg ccttctggtg 600
ctggccctcg agcccaaacc ctcaatccca atgccctcat ccatcctgtt tccactgtta 660
ctgatcatcg cagccagata tcaagccctg cctctttcga tttggggtct tcatccttca 720
tccagtgggg tctggcatgg ctggactctg tctttgacct ggtcatggtg gctgagtact 780
tcgatgagtc attggttctg ctggcagatg ccctgtgctg ggtctagat gacgtggtgg 840
gcttcatgca caatgcccag gctggacata agcagggcct cagcactgtc agcaacagtg 900
gactgactgc ggaggaccgg cagctgactg cacgggcccg agcctggaac aacctggact 960
gggctctcta tgtccacttc aaccgcagtc tctgggcacg gatagagaaa tacggccagg 1020
gccggctgca gacagctgtg gccgagctcc gggctcgccg agaggcccta gcgaaacatt 1080
gtctggtagg gggtgaggct tctgacccca aatacatcac tgatcgccgg ttccgcccct 1140
tccagtttgg gtcagctaag gttttgggct atatacttcg gagtggattg agcccccaag 1200
accaagagga atgtgagcgc ctagctaccc ctgagctcca gtacaaggac aagctggatg 1260
ccaagcagtt cccccctacc gtctcactgc ccctcaagac ttcaaggcca ctctccccat 1320
aaacatcaga ctacagattt aggtggaaga gcagccatgt ttgaagggca catgtgatga 1380
gtgggggca gcaagatgcc atttctgcat ctcccagaag ggatgagtct ttgtcccaaa 1440
tgcaagcccc ctcttcgctg ggctcccagc agtgcttccc tcctccaccc tccactcatt 1500
ttgttctttc cccccaactt tttttttttt ttgaaacgga gtcttgctct gtcccccagg 1560
ctggagtgca gtggcatgat ctcggctcac tgcaacctct gcctcccagg ttcaagcgat 1620
tctcctgcct cagcctccag agtagctagg attacagata cgtgccacca tacccggcta 1680
atttttatat ttttagagac agggattcaa catgttggtt aggctggtct tgaactcctc 1740
acctcaggtg atccacatga ctctgcctcc caaagtgctg ccattacagg cgtgagccac 1800
taggcctgac ctccccttcc cctttcctgc cccaaggcag atccacatca ccgaagctcc 1860
ctagaggggc aaaagatgga gtgagccaca ggaagtttgg ggcgtggtga gttggaatga 1920
tacgtccatt tctctatgaa atatttgcta ctagactgtt catttctctc tgacatgttt 1980
gttgaatgaa taaataattt gaaacttcaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2040
aaa 2043

<210> 122
<211> 2877
<212> DNA
<213> Homo sapiens

<400> 122
tcgacccacg cgtccgggat gaggcccggc ctctcatttc tcctagccct tctgttcttc 60
cttggccaag ctgcagggga tttgggggat gtgggacctc caattcccag ccccggcttc 120
agctctttcc caggtgttga ctccagctcc agcttcagct ccagctccag gtcgggctcc 180
agctccagcc gcagcttagg cagcggaggt tctgtgtccc agttgttttc caatttcacc 240
ggctccgtgg atgaccgtgg gacctgccag tgctctgttt ccctgccaga caccaccttt 300
cccgtggaca gagtggaacg cttggaattc acagctcatg ttctttctca gaagtttgag 360
aaagaacttt ccaaagtgag ggaatatgtc caattaatta gtgtgtatga aaagaaactg 420
ttaaacctaa ctgtccgaat tgacatcatg gagaaggata ccatttctta cactgaactg 480
gacttcgagc tgatcaaggt agaagtgaag gagatggaaa aactggtcat acagctgaag 540
gagagttttg gtggaagctc agaaattgtt gaccagctgg aggtggagat aagaaatatg 600
actctcttgg tagagaagct tgagacacta gacaaaaaca atgtccttgc cattcgccga 660
gaaatcgtgg ctctgaagac caagctgaaa gatgtgaggc ctctaaagat caaaacaccc 720
ctgtcgtcca ccctcctccc actccaggga ctgtggtcat ggtggtgtgg tgaacatcag 780
caaaccgtct gtggttcagc tcaactggag agggttttct tatctatatg gtgcttgggg 840
tagggattac tctccccagc atccaaacaa aggactgtat tgggtggcgc cattgaatac 900
agatgggaga ctgttggagt attatagact gtacaacaca ctggatgatt tgctattgta 960
tataaatgct cgagagttgc ggatcaccta tggccaaggt agtggtacag cagtttacaa 1020
caacaacatg tacgtcaaca tgtacaacac cgggaatatt gccagagtta acctgaccac 1080
caacacgatt gctgtaactc aaactctccc taatgctgcc tataataacc gcttttaata 1140
tgctaatgtt gcttggcaag atattgaact ttctgtggat gagaatggat tgtgggttat 1200
ttattcaact gaagccagca ctggtaacat ggtgattagt aaactcaatg acaccacact 1260
tcaggtgctt aaacacttgg tataccaggc agtataaacc atctgcttct aacgccttca 1320
tggtatgtgg ggttctgtat gccacccgta ctatgaacac cagaacagaa gagatttttt 1380
actattatga cacaaacaca gggaaagagg gcaaactaga cattgtaatg cataagatgc 1440
aggaaaaagt gcagagcatt aactataacc cttttgacca gaaactttat gtctataacg 1500
atggttacct tctgaattat gatctttctg tcttgcagaa gccccagtaa gctgtttagg 1560
agttagggtg aaagagaaaa tgtttgttga aaaaatagtc ttctccactt acttagatat 1620
ctgcaggggt gtctaaaagt gtgttcattt tgcagcaatg tttaggtgca tagttctacc 1680
acactagaga tctaggacat ttgtcttgat ttggtgagtt ctcttgggaa tcatctgcct 1740
cttcaggcgc attttgcaat aaagtctgtc tagggtggga ttgtcagagg tctaggggca 1800
ctgtggggct agtgaagcct actgtgagga ggcttcacta gaagccttaa attaggaatt 1860
aaggaactta aaactcagta tggcgtctag ggattctttg tacaggaaat attgcccaat 1920
gactagtcct catccatgta gcaccactaa ttcttccatg cctggaagaa acctggggac 1980
ttagttaggt agattaatat ctggagctcc tcgagggacc aaatctccaa cttttttttc 2040
ccctcactag cacctggaat gatgctttgt atgtggcaga taagtaaatt tggcatgctt 2100
atatattcta catctgtaaa gtgctgagtt ttatggagag aggccttttt atgcattaaa 2160
ttgtacatgg caaataaatc ccagaaggat ctgtagatga ggcacctgct ttttcttttc 2220
tctcattgtc caccttacta aaagtcagta gaatcttcta cctcataact tccttccaaa 2280
ggcagctcag aagattagaa ccagacttac taaccaattc cacccccccac caaccccctt 2340
ctactgccta ctttaaaaaa attaatagtt ttctatggaa ctgatctaag attagaaaaa 2400
ttaattttct ttaatttcat tatgaacttt tatttacatg actctaagac tataagaaaa 2460
tctgatggca gtgacaaagt gctagcattt attgttatct aataaagacc ttggagcata 2520
tgtgcaactt atgagtgtat cagttgttgc atgtaatttt tgcctttgtt taagcctgga 2580
acttgtaaga aaatgaaaat ttaatttttt tttctaggac gagctataga aaagctattg 2640
agagtatcta gttaatcagt gcagtagttg gaaaccttgc tggtgtatgt gatgtgcttc 2700
tgtgcttttg aatgacttta tcatctagtc tttgtctatt tttcctttga tgttcaagtc 2760
ctagtctata ggattggcag tttaaatgct ttactccccc ttttaaaata aatgattaaa 2820
atgtgctttg aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa 2877

<210> 123
<211> 681
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (101)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (223)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (224)
<223> n equals a,t,g, or c

<400> 123
ctccctctcc cttttgctgc aagactggat ctgctcttga atctgccccg gataattctg 60
ggcagcttct tcgatcaagc tgacattatg ggatttgtgg nccttggatt cacgacacac 120
aaaacagagg aacttcccat catcctcgca gaaatagtgg aacatctcct ggtgcctcgg 180
gcaatgtagc ctcttttcct tttggactgc acctcagagg ctnngtagag ctttggattt 240
tctccaccag attccgcaac agcgagttga acctgattgc gttcttcctt acggaagttt 300
tgcagagggg acatttgaaa aatccacatg atgtttcccc aatctgagtg atgcatttga 360
ggcagaaatt gtgcccacag tcgatggtga caggtttctg cagaatgtcc aggcagatgg 420
ggcagatcac ttcctcttgc agtttgttca caaactgccc actggccatg acagaacaac 480
agggctgttt caagactgta ggaagctgtg ccaagtctgt aggagccccg gagtccactg 540
tggatactgt ttctaggaag ggagaaggga gtcagagaaa gtggaggtca gagattctgc 600
ccaattagtt agaagagcag agagagagga aaagaagagg gagaaaaaaa taaagaaatg 660
atagaaaagc gtaaaattta g 681

<210> 124
<211> 606
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (34)
<223> n equals a,t,g, or c

<400> 124
ttgatggcca tttggaagta aatttccgca gtanttcata ggtgcactta acacagactt 60
tgcttaatga aaatgtcagt tctaatagta actgattcac ttctgaacag aagtgatttt 120
aggcatattt cttaacatat atcaagcaaa gtcctgttaa aagatctaaa tgaagaatgg 180
agacctcagt gattaaagat attttgtttc tgaccttgag cagattgctt acctgttctc 240
tagactataa cccaacatgt aaaaaaaatt tgaagatggt gatgaggaaa gtgagatata 300
tatatatata tgtattaygt ttctagcact tttccctttt aaaaagtgaa aatatccttg 360

tacatttttg aaaaatatat ttycagtyct gaaaaatgta gcagaagtag tgaaaatgyc 420
atattttaaa tgttgattat tagataaatt taacctgctt agggtttatt gtaactacac 480
ctttcagacg tgtgtttygg agtagtggaa ttgccagcca ggccctgtgg cttggaaagg 540
catcccagaa atcctcggcc agaaggtgtg gcttgttaaa gcattgagat tcmgagtatt 600
ttggtt 606

<210> 125
<211> 1211
<212> DNA
<213> Homo sapiens

<400> 125
aattcggcac gagagcggcc ttcctcggtc aagtcgctgc gctccgagcg tctgatccgt 60
acctcgctgg acctggagtt agacctgcag gcgacaagaa cctggcacag ccaaytgacc 120
caggagatct cggtgctgaa ggagctcaag gagcagctgg aacaagccaa gagccacggg 180
gagaaggagc tgccacagtg gttgcgtgag gacgagcgtt tccgcctgct gctgaggatg 240
ctggagaagc ggatggaccg agcggacaca agggtgagct tcagacagac aagatgatga 300
gggcagctgc caaggatgtg cacaggctcc gaggccagag ctgtaaggaa cccccagaag 360
ttcagtcttt cagggagaag atggcatttt tcacccggcc tcggatgaat atcccagctc 420
tctctgcaga tgacgtctaa tcgccagaaa agtatttcct ttgttccact gaccaggctg 480
tgaacattga ctgtggctaa agttatttat gtggtgttat atgaaggtac tgagtcacaa 540
gtcctctagt gctcttgttg gtttgaagat gaaccgactt tttagtttgg gtcctactgt 600
tgttattaaa aacagaacaa aaacaaaaca cacacacaca caaaaacaga aacaaaaaaa 660
accagcatta aaataataag attgtatagt ttgtatattt aggagtgtat ttttgggaaa 720
gaaaatttaa atgaactaaa gcagtattga gttgctgctc ttcttaaaat cgtttagatt 780
ttttttggtt tgtacagctc cacctttag aggtcttact gcaataagaa gtaatgcctg 840
ggggacggta atcctaatag gacgtcccgc acttgtcaca gtacagctaa tttttcctag 900
ttaacatatt ttgtacaata ttaaaaaaat gcacagaaac cattgggggg gattcagagg 960
tgcatccacg gatcttcttg agctgtgacg tgtttttatg tggctgccca acgtggagcg 1020
ggcagtgtga taggctgggt gggctaagca gcctagtcta tgtgggtgac aggccacgct 1080
ggtctcagat gcccagtgaa gccactaaca tgagtgaggg gagggctgtg gggaactcca 1140
ttcagtttta tctccatcaa taaagtggcc tttcaaaaag aaaaaaaaaa aaaaaaaaaa 1200
aaaaaaaaaa a 1211

<210> 126
<211> 881
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (7)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (16)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (34)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (37)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (41)
<223> n equals a,t,g, or c

<400> 126
tatgatncct cgctcngttt ctgaaatttt cacnttncac naggtttcaa catataaact 60
ttcaggggac acagacattc agactatagc accaagctgt agaagctaca tagttgtaga 120
ccagggtcag caacccaaga agcctgactt ccaagctgtg cttttaactt ccccaccatg 180
ttgcacctaa agctttggag ttttcctgtg attagtgttt ttggtgttgt tttatttttt 240
ttcttacagg aactcttgca agaagaaagg actatgrgkt cmactttaga gggasccatg 300
gggmctaaac maaattctka ggccccctca accatctaaa tggacttcct tctgggccag 360
gacactcgaa aattaaacct gaaagactgg ttcaggccat gatgggaagt gggagtcgaa 420
catgcctcat catacccctcc agcattaaca tcaacacaga ccttaaggct gataagaagc 480
atttacaatc tattctctct gaagtcttct acctggaggc ttcatctgca tgataaaact 540
ttggtctcca caacctctta caacccaggc attcctttct atcgataatt actctttcaa 600
ccaattgcca atcagaaaat tgttatatct acctataatc tagaagcccc cacatcaagt 660
tgttttgcct ttctggacag gaccaatgta tatcttaaat gtatttgatt gatctctcat 720
gtctccctaa aatgtataaa accacgctgt tccccgacca cctggagcac atgttctcag 780
ggtctcctga gggctgtgtc acaggccatg ttcacttaca tttggctcag aataaatctc 840
ttcaaatatt ttaaaaaaaa aaaaaaaaaa aaaaaactcg a 881

<210> 127
<211> 917
<212> DNA
<213> Homo sapiens

<400> 127
ccatcttcac attttgcttc catatttgaa gagtctcacg tgccagtaat tgaagaatct 60
ttgagagttc agatatgtga aaaggcagaa gaattaaagg acattgtgcc tgaaaagaaa 120
agcactttaa atgaaaatca gcctgagata aagcatcagt ctcttctcca gaaaaatgtg 180
agtaagaggg atccacccag cagtcatggg cacagtaaca agaaaaatct attaaaagta 240
gaaaatggtg ttacacgaag aggtagatcg gttagtccca aaaagccagc cagtcaacat 300
tcagaggaac atttggataa gattcctagt cctctaaaaa ataaccccaa aagaagaccc 360
agagatcaat ccctcagccc cagcaaaggg gaaaataaaa gttgtcaggt cagcaccagg 420
gcaggctctg gacaagatca gtgcagaaaa agcagagtcg tcgccagccc aaaaaagcag 480
caaaaaattg aaggaagcaa agctccatca aatgctgagg ccaaattatt agagggtaag 540
agtcgaagaa tagcaggcta tacgggcagt aatgctgagc agatcccaga tgggaaggaa 600
aaatcagacg tcatcaggaa agatgcaaag cagaatcagt tggaaaaaag cagaacaagg 660
tctccagaga aaaaaatcaa aagaatggtt gagaaatctc ttccatccaa aatgactaat 720
aagactacaa gtaaagaagt atctgaaaat gaaaaaggaa agaaagtaac cacaggagaa 780
acaagttcta gtaacgataa aataggagaa aatgtccagc tatcagaaaa gaggctgaag 840
caagaacctg aagagaaggt agtttcaaac aaaacagaag atcacaaagg gaaagaacta 900

gaggcagctg tacaaaa 917

<210> 128
<211> 1287
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1142)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1233)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1265)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1271)
<223> n equals a,t,g, or c

<400> 128
tttaaaaacc cctggaggtt ttaaccttgt gatgccttta tgaatatcct gttgaaatat 60
ccttcccccct atgccttata aaccagagaa agccctttga agccttataa tgccaatgga 120
agatacttag aagtaaacaa aatagagagg tatatgtaga ttttcttagg tcattagttt 180
gtgtctttgt ctggtaggct gaaactactg tcatatgact ctctccctgg ccagatttta 240
atagtcatac taatactgat gtgaatcctg ataattaaac tatcttgtca ttacatttgt 300
agataaagtt ttggttagaa atgattttgt atgtgttagg tatggtaata cagtctcaaa 360
taaaaggtca tgttaagata aaaggtcatg cttacttttt aattaatttg tgtaataaaa 420
tttaggtctt tggaaaactt atttttcaaa taaatgaacc tttcaaataa aaaagagaat 480
tagtttaacc tttatctcat ttcctattat aggggtattg aatggacaag tttgactagt 540
tttctttctt ttgctacctc aacaccaaac aatatgggat tagtgagaaa tgaacttcaa 600
ctggttgatc ttccaacagg tttgttttta aagatccaaa taggtttgtc atattgaata 660
aacatgttgc catttataaa acatgtttga aagtacttct ttcaccttgg aatttttttt 720
tatatttcat gcttatatat ttatyctttt attctctaat aattgcccta gaaaggcctc 780
atcattgttt acatggaaat gttgttggca caaatacatg gtaaaatgga ggaccattag 840
cctgaamaga cagattcatt aaaaaatagg ataccggttc tacttttaag tgcattgtta 900
tatgtaacca actttaaaag atcgatttaa aaataactct gtcaatggac tttattagag 960
tctgtgctgg aaattttggc ttttatagga aacacttaga aaatttatag gttaaggatt 1020
gtttttaaat gctcaaattt aaaacttgta atagtctctg gcygaatgga atagagaaac 1080
ttaatttggg attttgaaga ttctacagta ggaaacgtcc ccaataaggk aactttttca 1140
gnaattggaa agcctaaacc ccagtgaatt tccaaaataa rgaatttgga aaattataaa 1200
gggraagrgg ttccaaatta ttttcctggg ggnatgcagg aaggttccaa aagagggttt 1260
ttttnaaaat nacaattgtg atgaggt 1287

<210> 129
<211> 603
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (391)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (517)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (580)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (602)
<223> n equals a,t,g, or c

<400> 129
cgcttgggct tggcgggtat aggttgcagt gagccaagat ggtgccactg cactgcagcc 60
tgggtggctg aacgagactc cgtctcaaaa aaaaaatcta aatctgacat ttgatgctat 120
ttttattaat attggaatgt tctgtcttga actttattca atataatcaa gaataaagat 180
agagtaaacg tcactgattt gtactattaa gagagaaaaa atatgccaca caactaaaca 240
taggtttaaa ttatgaagaa atttagaata gaggtttatt agatttaggg aacactaaga 300
acaaaaaagg aaggagtgat acctgcctga gtggacagct gtaaatcagc tgtaattact 360
gcagttgtwc caatagttgt gartggctcc nagtcmcttt argagtcctt ggaartwctt 420
ggtacacatt tgttggctgt wccttaaagg aartggcaar tccagtttgt tcyctctacc 480
acactaract gccactgaca agtttgggtc tgttggnttc aaaattttgt aagccatttt 540
cacaagtaca aagatacatt ttaaccttgt cttctccaan attactgagt aggaatttta 600
tnt 603

<210> 130
<211> 532
<212> DNA
<213> Homo sapiens

<400> 130
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ataatgtttt tcttttcttt ctttcctttc ttttctttct tttctttact tttttttttc 120
ttttcttttc tttttttttt tttgacaggg tctggctcta tagtccaggt tgagtacagt 180
ggtgtgatca cggctcactg caaccttaac ctctaggctc aagtgaccca cctcagcctc 240
ttgagtagct gggaccacag acacaccacc atggccagat agttttctgt atttttttctt 300
tgtagagaca gggtttcacc atgttgccca ggctggtctc aaactcctga gctcatgtga 360
tctgcctgcc tcggcctccc aaagtgctgg gattacaggc atgagccacc acatgtggcc 420

cattttttct tcataagtga gtttgtagtt tttactttgt tctaattttt tgaggctatg 480
ttcaggaagc catacagctt gaataagtaa ccatctcagg agaaaaaaaa aa 532

<210> 131
<211> 776
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (630)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (669)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (769)
<223> n equals a,t,g, or c

<400> 131
aatcctcagc cattttgtga aaatagccaa gaaacttcta gaactcaaca accttcattc 60
tctcatgtct gtggtatcag cattacaaag tgctcccatc ttcaggctga caaaaacctg 120
ggctctttta aatcgaaaag aagactacct ttgagaaatt ggatacctga tgtcgaaaga 180
agrtaattac aagcggacac gggaatatat ccgargcctg aagrtggttc caagtattcc 240
ctatctagga atctatcttc tggrtttaat ctacattgrt tctgcatatc ctgcctcagg 300
agtaatcatg gaaaatgaac aaagatccaa tcagatgaac aatattcttc gaataattgc 360
tgatttacaa gtttcctgca gctatgatca cctcaccacc ctgccccatg tgcagaagta 420
cctgaagtcc gtacgctaca ttgaagagct ccagaagttt gtggaagacg acaactacaa 480
actgtcgctc agaatcgaac caggaagcag ctctccaaga ctagtctctt ccaaggaaga 540
tcttgcaggt ccctctgctg gctccggttc tgcgaggttc agccggaggc acctgtcctg 600
acacatctgt tgctggcagc ctccccacan ctccagtgcc cagacacagg gaagagccac 660
agcctaggna acaatatgga tgtgttcagt tgagtgttag ttgaggagta aaagtgcgac 720
atttcccttc ggagaaaggc aagggcacct acttggacga cagtgttcnt agagtt 776

<210> 132
<211> 689
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (348)
<223> n equals a,t,g, or c

<400> 132
atcagggacc cttttgatcc aattatagtt attgggcaga tacagtagta ccctattatc 60
agaagaccta gtttcaaatc ctgagtcaat ttctaattca ctgtgtgacc ttgtacaagt 120

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cacttaagct ctctgatcat tggttcaaca tctttaatat gaggagagta atgcctatct 180
caattacctc ataaaattat tgcaaagatc aagtgagttg atatgttaca aattatttct 240
aaattataag attctgtata agtggaaggg ttaagtatac tcccatatta ttaaacaccc 300
tacgtatcac tcaggattct atatgactct gagttctcaa tttctagnaa atggtcccat 360
ttttgctttg ttccctacaa ttctacggag tctttttttt ttwaaaggaa gggtgtaggc 420
aaaggtaaat gggagaaaac atggaatcac ataccactct ttggtgctgc taggcaagaa 480
ttttaaactg agtttaggtc accatcgtgg acttaaggtc catatcacct cagggagaca 540
agtagagtgg gaggcatcca aaaggtaggt gattcttctc ccctctagtg aagaatacaa 600
ggtcaattta caaaaaagca ccagcagcaa ataattggaa aattaaattc ataaamcatt 660
tataatagcg tcaaaaaaaa aaaaaaaaa                                  689
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<210> 133
<211> 555
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (4)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (36)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (308)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (471)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (484)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (489)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (510)
<223> n equals a,t,g, or c

<400> 133
ttcntgcccg ccccatcctg tgctttggcg taggcnatca ctgaagactt tctatttctc 60
cattagttca ttcatcttgg tagctagact catgacggag ctgctgccac cccagcagat 120
ctgctcgcct tgctgcttct tcacggtctc cacggccttc gcagaggtgt cagcaactgc 180
catgaccact tgcagcagtt ggctgtagga agtcagattc tggtgcgtgg cctggatgat 240
ggggccgcac gggtggaggt cagggcctgg gcgctggcag cactcgccca gctcgtcgtc 300
gtagattngg agaaaagcca agattagctg gtggaagtcg gaagtgacca gacgcagctt 360
ctggtctagg gtgctgatgt cggctgcgcc cgcaaarccc cttgcttcat gctgtgcaaa 420
ktactccgtt tctaaagcgc gtgcaattgg gcagcattct cctggcagtg nctgggcaac 480
ttcngccanc tttttcttct tcttcggaan ttggcaaagg catgggccca atggccatca 540
tcaatctggc ttgtt 555

<210> 134
<211> 790
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (776)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (780)
<223> n equals a,t,g, or c

<400> 134
gcaagaatat aaaattctga ggcctatttt agctctaagc cagaccatgt tataacttct 60
taactgaata cttcttatct atactttttt tctatatctt tccatctatc tgtaagtagc 120
ttttcccatg atctgacttg tttatatttc ctattaactg acaaagcatt taaaaacagt 180
taaaaattgt ctcgacaggc attttaaatg tcaagacatt ataaaatact ttagatttat 240
acagcaattg tgaacacctt tgacaaatga acatgtctgt tcagcctttt tggtacccct 300
ttttattttg cttaggtaga tcaaattcta agttgatctt ttctagcagc agggtcagag 360
tctagtgatc gtttttaaaa tggcttagat gctacctttc ttttctgaga actcagtgtg 420
atataatcct tataagatat tgacagctaa ttttatggat tatcctaccg ggacagtgga 480
acctaagtag tttgaagacg araaattgtt ttgattcaka agcaatgggt tcactagtga 540
aaggaaagat cccacgatcg taagtggtaa atgtttatat ttgttgaata actctctgaa 600
aaaaggaaat aaagtagatt agccttggta agaggtggct taagagtggt tttatgaatc 660
taagttttat ttgaaaaatg tgtgaacttg tttaaggtaa atgtgagaat taataaagga 720
attgagaaga aagatatttg atcgtttttt ggaataacat ttacccaatt taagangttn 780
aactactttt 790

<210> 135
<211> 1408
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (116)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1364)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1381)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1393)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1399)
<223> n equals a,t,g, or c

<400> 135
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gaagaaaaat tttgtctgat tatgtgaagg atctttctgt acatgaaaag aagggnaaat 120
aaacttgcaa ttgaatagac tgattatagt agcactgaga cacaaaaaga ttgaccatgt 180
tgccctccag acactcatac aaggtcgtgg acaccaggtt gaaggcggac tatttagggt 240
ggtaaaggaa ttatgattgt tcttgagcca aagtaattta gtttgaatat aatgaaacat 300
accctgtaaa gactgctaga aagtaaaagg attcgtcttc agaggttgta gaaggtgccc 360
ttcttagtta aaaccaaact gggaaaagta atactggata aaatattcag gataaatttt 420
gcctcagcag aatttcaaag ggcagttgtt cctctgtttc attattgaat sttcagaata 480
tagttaaagc caaargctta aaatatgtta aatgtttcac ttataaccat aatcttttta 540
catagagcat actctgcctt cataataact aaatcctctg catgtggtag atgagtacgt 600
ttaggaaata ttgtcagtgc aattaaatgg cctacacttt aaacagtatc ataaaaacaa 660
atccttaaat atattctact tgagtcacaa aagctgaaca acagaaaggt gttttgtttt 720
tgcctttctc acagtgttgt ggtgagaatc agatgagata gtatttkgac taaacacttc 780
tgaaattgta aatatatggt ggcattattg ttcttatgtc ggcttaggag gataccaaag 840
gggaagttaa tggtcacagt gcacttatgt agctttctaa gctactcaat gtgattcttg 900
ttctctttgc tgttcttttt ctcctccccc atggtgtcct tcagagagaa aaggaatgta 960
gataaatgaa tccctgcaga tgtgtcctga catttcaggg agggacaggg tataatgatg 1020
ccatcctgca aaggcagcct gtgtgagaaa aagaaatcaa ataatgtgga ttttaaaatt 1080
acaaaagaca ttcatttgca gtttatgaaa ggaaaatgta gtttggatac aaagctgatt 1140
aaattggatc aagaaatatt agaattaaat gcaaaaaata atccatgcat ttatggtttt 1200
gatttttata tattcccagc tagttgaaaa tggatgattc ccacaagaag cataactcag 1260
cttggttcct gcttaccgga gtatttccac tatggtatat attgatacat tccttccatt 1320
atggtaggtt gtataccaga ggtaccagtt accggtgggg atcntaattg gaattttggc 1380
ncccggggtt ccnggggganc ctttacaa 1408

<210> 136
<211> 902
<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (814)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (902)
<223> n equals a,t,g, or c

<400> 136
aattcggctt tcgagcggcc gcccgggcag gtacttataa ttttggcctt ctgcactact 60
cttttgctct tacgaacata atggactctt aagaatggaa agggatgaca tttacctatg 120
tgtgctgcct cattcctggt gaagcaactg ctacttgttc tctatgcctc taaaatgatg 180
ctgttttctc tgctaaaggt aaaagaaaag aaaaaatagt tggaaaataa gacatgcaac 240
ttgatgtgct tttgagtaaa tttatgcagc agaaactata caatgaagga agaattctat 300
ggaaattaca aatccaaaac tctatgatga tgtcttccta gggagtagag aaaggcagtg 360
aaatggcagt tagaccaaca gaggcttgaa ggattcaagt acaagtaata ttttgtataa 420
aacatagcag tttaggtccc cataatcctc aaaaatagtc acaaatataa caaagttcat 480
tgttttaggg tttttaaaaa acgtgttgta cctaaggcca tacttactct tctatgctat 540
cactgcaaag gggtgatatg tatgtattat ataaaaaaaa aaacccttaa tgcactgtta 600
tctcctaaat atttagtaaa ttaatactat ttaatttttt taaagatttg tctgtgtaga 660
cactaaaagt attacacaaa atctggactg aaggtgtcct ttttaacaac aatttaaagt 720
acttttttata tatgttatgt agtatatcct ttctaaactg cctagtttgt atattcctat 780
aattcctatt tgtgaagtgt acctgttctt gtcnctttttt tcagtcattt tctgcacgca 840
tccccctttta tatggttata gagatgactg tagctttcgt gctccactgc gaggtttgtg 900
cn 902

<210> 137
<211> 730
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (606)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (647)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (671)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (685)
<223> n equals a,t,g, or c

<400> 137
tacttcagat acactagtaa agcctgctgt attccaacta atgaggacag atatgtaata 60
tatatacatg tatatacgta tgtatgtata tatactatat atataattat actttaagtt 120
cctaaggtac atgtgcagaa tgtgcaggtt tgttaaatag gtatacatgt gccatggtgg 180
tatgctgcac ccatcaaccc atcatctaca ttaggtattt ctcctaatgc tatccctccc 240
ctagccaccc acccccagac aggccccgct gtgtgatgtt cccctccctg tgtccatgtg 300
ttctcattgt tcaactccca cttatgagtg acaacatgcr gtgtttggtt ttctgttcct 360
gtgttagytt gcwgagaatg atggtttcca kcttcatcca tgwccctgca aaggrcatga 420
actmattctt ttttatggct gcatagtatt ccatggtgtk tatgtgccac gttttcttta 480
tccagtctat cattgatggg catttgggtt ggttccaagt ctttgctatt gtaaatagtg 540
ctgcaataaa catacacatg tctttatagt agaatgcaca tgtctttata gtagaatgat 600
ttatantcct ttgggtatat aaccagtaat gggattgctg ggtcaanggg cattctggtt 660
caagatcctc naggattcac cacantgtgt tccacataat ttaagctatt ttacactccc 720
accagcagtg 730

<210> 138
<211> 524
<212> DNA
<213> Homo sapiens

<400> 138
ggcagaggag gccactgtgc ctggtcaaga aatggaactc ttacacactg ctggtgggaa 60
tgtgaaatgg taagccactt cggaaaacag tttgacaatt tcttatgcta aaaatacacc 120
tatcagatra tttagccact tctaggtatt tacttaagaa aaaataaggc atacatccat 180
atgaaractt gtaaataaat gttctcatta tttttatttg aaatagctma aactggaaac 240
aacccaaata tccatcagca agtgaatggr taaacaaatt gtratatttg tatgcaatat 300
aacaccactc agtaatatga aaatgaacta ctgatgtttg caaaacgttg aaattcaaaa 360
taattatgct gagtgacaga atccagacca caaataatac ataatgtwtt attctattta 420
cataaagttt tagaaaaatc caaactaatc ttartttacc aaagccatac caatggtata 480
tggggcttgg ggcagkttaa acsgattatt gaaaaaaaaa attt 524

<210> 139
<211> 869
<212> DNA
<213> Homo sapiens

<400> 139
ctgattcctc ctcacatatg aaaagtgaaa gttgtgagtt gttttcctct tatttaaaca 60
ttggcctatt ataatctgtg ttggttattt ttctcctgta agcatcctga tttttctgta 120
ggaacttttc tttaaatgac acacattgcc acttgtgtag atatttttaa gttctttggc 180
taagtcctct cctaactgcc tgtcctctgg ttaggcccct ccctctccac tagtggtgaa 240
tgcatgtgtc tgtctgatca gcatcactgc acacggaggt ctagtgagcc tcttgctaag 300
tgtcacacac actcttccca aagacgtgat gagttaaagt tgtattctga aatcatgaag 360
ccagagcctg tgccagacct tctgctacct ctcatagaat tgctctgtaa ttctaaattt 420
aaaattagaa gtagagagag ataagccatc gccccttttgc ctctgagaat tggctgctgt 480
ttctaatata attattttct aagatagcca gatagttaga aaaagatttt cattgatgac 540
atatctttaa actttcttgc atcagtattc taaattgagc aaactgaaag attttcatca 600

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ggaaaggagc actgtgggaa gagcccagta ttcacatttt ttccccattt ttcagaagcg 660
acatttcata tataggtgcc aaaagtgaat cggggtgcgg agagtgggaa ccttttgaat 720
ttatgattgt cacagagatg gtagaaatta tgatctgact ggaaaacaat cctgtatccc 780
ctcccaaaga atcatgggct ttttttttga attaaaaagc agacaaatag actttctcgg 840
gaaaaaaaaa aaaaaaaaaa cgcggccgc                                   869
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<210> 140
<211> 586
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (5)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (439)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (563)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (577)
<223> n equals a,t,g, or c

<400> 140

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ggggnaccag cgcgggtgcg cagacgaaag gcgctctttg ccagctgaaa gttcccacgg 60
aaaaactacc atctcccctg cccaccatgg cagacgaaat tgatttcact actggagatg 120
ccggggcttc cagcacttac cctatgcagt gctcggcctt gcgcaaaaac ggcttcgtgg 180
tgctcaaagg acgaccatgc aaaatagtgg agatgtcaac ttccaaaact ggaaagcatg 240
gtcatgccaa ggttcacctt gttggaattg atattttcac gggcaaaaaa tatgaagata 300
tttgtccttc tactcacaac atggatgttc caaatattaa gagaaatgat tatcaactga 360
tatgcattca agatggttac ctttccctgc tgacagaaac tggtgaagtt cgtgaggatc 420
ttaaactgcc agaaggtgna actaggcaaa ggaaatagag ggaaaataca atgcaggtgg 480
aagatgtaca ggtgtctgtg catgtgtgca atgagtggaa gaatatggct gtagccataa 540
aaaccctgtc aaataaaacg ggnaacattc aggccangga ccactg                586
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<210> 141
<211> 614
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (546)

<223> n equals a,t,g, or c

<400> 141
aaataaaaag gcagtggccc caccacattt ttttcagcat agtagctggc attttgttat 60
cattagccag agtagcttca gcatataagt tattgatgtt ttccaacttc aaaagtgcat 120
tttatcctcc cagtaaattt gataatgatt tgtcacagct ttgtcatctt ttgacttttg 180
cttatgggcc tcacttcgta caactataac atgaaaaagg attgtcctaa agtaagggaa 240
tcagttaatg gtaggatgaa gaaactgtaa aaactcctag aaaaaaaacc tgtgtgcatt 300
tttctggaaa gttttcaaac tgtgtaattc agttttcatt caattatata atttggttat 360
atgctttaaa aaacatttgt ctaaatgttc ccggttttct tctggtctta gagtcagctg 420
agtgctggct atgcagccac tcgtattttt gcatccagaa aggagtaact ccctttatat 480
gaagrttttt tttttaagct tagatgctat gtaaggagaa aactatttgt aatcacatag 540
tacccngggr ggggagtgrt ggatgctttt ttaaaaaagg rtatttaagt atattatgta 600
atttaaatat aaat 614

<210> 142
<211> 574
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (19)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (522)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (574)
<223> n equals a,t,g, or c

<400> 142
ntgttaagtt ctgacattng gagaaaatac attacaaaga acaggagctg gtttttggtt 60
ttccttgtgg ctgtgttttt gaattgaagg gatgtgggat ggtggtgaca gaagtctgag 120
catagtttct gaataattgg aggggagatg ggcattcttt gggactatgt ccgcattaca 180
ttgagttttc tccctctagg aagagagagt ttgtgtttta ttttctgtaa gtaaaagcta 240
catgtttagg atttttaaac catattaatt gttatatttt gtatttcata attatattat 300
gtgttagtgt gtactggaat aacatgtttt atttggttag ttggtgcaaa agttttctaa 360
atctactgct gtattagaaa ctgaaaaggg agggaaattc cagatgtttg atgggaacat 420
cactggtgaa tatctaggrt tggtaagtag acycaaggtt gaagragtaa ggtggggtta 480
acccttaata ttaccttkgg tatatgcccg tttttagcac cngaatcacg ggggtccttt 540
gttccccaac cttaacagca gcccctgtct ggtn 574

<210> 143
<211> 2012
<212> DNA
<213> Homo sapiens

<400> 143
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gcggccgctc tagaactagt ggatcccccg ggctgcagga attcggcacg agtgtagagc 120
tcaaagaaat ctgccaacat gtatgtggac tcttgagagg tgggctttcc cagtacatgc 180
taaacagact tgttatgcca agaggaagtg aatagaaatg atagcatcaa atatccaaac 240
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tccaggatat cttggccctc tgcctctggc tgctccctgg tgtttggcac catagcgttg 360
tcacttacaa ccattgcctt gggacacaca gagtgaactg tttgagtgat aagtaattta 420
ggtagaaact ttacccttaa tttcaaatga taccaaacag ctcattacta ccccaaggga 480
cgctctccgt agcttctgga ttccccagtt tccttctaga aacaaggact ccaatagcac 540
tataacccta aacaggccct aacccagaag aatacaccac aaaatgcgat tgattttctc 600
aaaatatcac agtcttagac actatacaaa taattcaaga aaattctttc taccctgcag 660
tggatatagt attctattat attctccagc aaaactttta ggacttttca aactcatttc 720
taagccaaat agtttagata aatatttacc cttatatttg gggggaattc aggctcacca 780
tttgccgagg caagcccatc aacagtctag aggcatattc tgtgtcattc cttcccgtct 840
ccttcataga atactacttt ttccttttgt ctcctggcca ttctccatca tctgctgatt 900
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ccaatacact cttatcacag tggttattgc ttcttactct tttcaaatgc attattctac 1020
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tagaacatgt tctagaaata gtggtacctt gctgctatta tacttagtaa cttatacccc 1320
aatataataa taagtattaa atacagattg tgtatgcatt ctttgtgtgt atatgccaac 1380
tgtactactt aacctcactg atgagcaatt agaaaaatac acaaattgtc atagtgaaaa 1440
taagtcttgg tcaattcaga tgatacgtga acctgataaa tgctctaata gatatgctat 1500
tttgtcctgt attgcttgtt ttacagtatg gtgcatgttg tttgctaagt aaaatgataa 1560
taataataaa gtataccaat tttaaggtta gaattaaaat tttgcacata tgcttcttga 1620
tattctgaaa tgtattctgt ggcttaatta tcttattcat acacatttca ctttggcttt 1680
ttacccctag gaaataactg tccaagtata tatctcgtct tctttcttgt aactttgatt 1740
aaactgctta cttcaactta caacattgta aagccagaat acctcatttt aacagtgaaa 1800
aaaaatatga tgacctgatg tgttctcttg tatttgattt gaactaccta aataggctta 1860
actgtaataa taaatataca attttggcag gcatttttc ctttgtttgg atgaacattt 1920
tgttattggt ccacttctaa ttttgtctta aagagttata aactcagtgt caataaaaca 1980
tcttgttata taaaaaaaaa aaaaaaaaaa aa 2012

<210> 144
<211> 558
<212> DNA
<213> Homo sapiens

<400> 144
aagtttttc ttaccccatc ctagtgagtt tgaaagtggg cctgaccaga atgtctcttt 60
cccatttgc cccgtttgaa ttaaatataa tgtctactct ttaaaggctg aaggggtggg 120
tgaggggatt gtttctcatt ttgtctccca agtcattttt ctgctgtgaa atatgaccag 180

gcttgtagga agactcatct tggagaaaat gtgaagtaat caaattgctt gagattagtc 240
tcctattgta tattagagcc aaaacacatr ataactttgg caacagggag ttgtctagac 300
tcaattttca gaggtcccat tgtagtgagt taatattgct aatcatgtca atcacttgac 360
akggaagtca gtggcaaatc tttaaagtat gcatttgata ctggcaaata tatactactg 420
atgtttcaca aaagaatctt agaatctgta gaaaacatta attacttcca tgaattattt 480
ctaaagtata actttaaagt tttgattttt ctatttaaat aaaaagcyat kgatgkgttt 540
agcakgtccc caaataga 558

<210> 145
<211> 1026
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (182)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1007)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1014)
<223> n equals a,t,g, or c

<400> 145
gcatttatat cctgttaagc attaatagct aatcactggg acttgaattc tgatggcaga 60
tagtctcttg cttagtgaga tggagttaac tattttttag taggaagtga gaacagctga 120
ttttcatgcc acgtttcata gccccacttt tggtagacta ccaccacgct kcttcgcgta 180
anagtyggca tcttgggaat gaatgcccag ccgctcgtgg gttggtgcaa agaagtataa 240
acatatatca ctaaggaaaa agaaagtttg tcttgccctt ctgacacagt gtgtgcactt 300
caggcaattt ttggaaaata taaaaaattc caawttctgc ctttcagcag catcaattgc 360
taggaacatt tcattcattt ccctgtaata ttaatgttct ttaagcataa tcactaatta 420
taagttgtat cctatttttt tccagcttaa tttctgtggt ttattgaaaa ccaagtataa 480
atgtgactaa aagcattttg ctttgttttt atagttaact ttcytaaggt tatggacatt 540
twataatgta acatttgatt ggcctggcct cttgacaatt cccttctagt tatgcatatc 600
ctccctgttg cccacatttc ttgttttaaa actcagtttc ttgttttcca gttgttgcta 660
tgtataacac ccatcttgaa agagagtata taggaagtta ttcagataac ttttgtagta 720
gtgatattca actatagcag taccttaact catgatgagc ttaggaacat aaaagataat 780
tgttgcttga atagcacccc cagagatact gacctaattg gtctggggtg gagatctggc 840
atggtagttt ttttcaagct ccaatcatcg gccagacagt tgctttatgt aggtttttaa 900
atgccaaagg cagatatgaa gtagatttaa ttaagacttg acttcagcaa tacaggggaa 960
cttaaaatac ttrtttttct ttaaactgca ggagtcactg ttaggtnttg cttnaaaaaa 1020
ttgcat 1026

<210> 146
<211> 521
<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (440)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (474)
<223> n equals a,t,g, or c

<400> 146
gggacctggc aagcggcggc tgcagggcag gtccaggggc cacatggctg agggggacgc 60
acggagcgac cagaggcaca atgaggaaat tgaagcaatg gcacccattt atggcgagga 120
gtggtgtgtc attgatgact gtgccaaaat attttgtatt agaattascg acgatwtwga 180
tgaccccmaa tggacacttt gcttgcasgt gatgctgccs aatgaatacc caggtacagc 240
tccacctatc taccagttga atgctccttg gcttaaaggg caagaacgtg cggatttatc 300
aaatagcctt gaggaaatat atattcagaa tatcggtgaa agtattcttt acctgtgggt 360
ggaggaaaat aagagatgtt cttattacaa aaatctccag gtgacagaac caggcccaga 420
tgttaaagga ggaaaactgn aggaggaaga tgttggaatg tggaaggtgg atcnccattt 480
ttagcatgtt cagccgggaa agttcggttt aaaagcattg g 521

<210> 147
<211> 557
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (17)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (527)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (543)
<223> n equals a,t,g, or c

<400> 147
ggattaacca ttaaatngat tgaaaaggaa actttgcacg gtatgagctt catacccccca 60
ccaaacaaag tcttgaaggt atttatttta ccaagtatat ttttaaagtt gttttataag 120
agagactttg tagaagtgcc tagattttgc cagacttcat ccagcttgac aagattgaga 180
ggcccatgcc aacagtctaa tctaagagat tagtctttca aactcaccat ccagttgcct 240
gttacagaat aactcttctt aactaaaaac ctagtcaaac aaggaagctg taggtgagga 300
gatctgtata atattctaat ttaagtaagt ttgagtttag tcactgcaaa tttgactgtg 360
actttaatct aaattactat gtaaacaaaa agtagatagt ttcacttttt aaaaaatcca 420

ttactgtttt gcatttcaaa agttggatta aagggttgta actgactaca gcatggaaaa 480
aaatrgttct tttaattctt tcacctttaa agcatatttt atgtctncaa aagtattaaa 540
aancttttaa tacaagt 557

<210> 148
<211> 1023
<212> DNA
<213> Homo sapiens

<400> 148
ggcacgagga accaccttct gtaggacagt caccaggcca gatccagaag gcttgaggcc 60
ctgtggtccc catccttggg agaagtcagc tccagcacca tgaagggcat cctcgttgct 120
ggtatcactg cagtgcttgt tgcagctgta gaatctctga gctgcgtgca gtgtaattca 180
tgggaaaaat cctgtgtcaa cagcattgcc tctgaatgtc cctcacatgc caacaccagc 240
tgtatcagct cctcagccag ctcctctcta gagacaccag tcagattata ccagaatatg 300
ttctgctcag cggagaactg cagtgaggag acacacatta cagccttcac tgtccacgtg 360
tctgctgaag aacactttca ttttgtaagc cagtgctgcc aaggaaagga atgcagcaac 420
accagcgatg ccctggaccc tcccctgaag aacgtgtcca gcaacgcaga gtgccctgct 480
tgttatgaat ctaatggaac ttcctgtcat gggaagccct ggaaatgcta tgaagaagaa 540
cagtgtgtct ttctagttgc agaacttaag aatgacattg agtctaagag tctcgtgctg 600
aaaggctgtt ccaacgtcag taacgccacc tgtcagttcc tgtctggtga aaacaagact 660
cttggaggag tcatctttcg aaagtttgag tgtgcaaatg taaacagctt aacccccacg 720
tctgcaccaa ccacttccca caacgtgggc tccaaagctt ccctctacct cttggccctt 780
gccagcctcc ttcttcgggg actgctgccc tgaggtcctg ggctgcact ttgcccagca 840
ccccatttct gcttctctga ggtccagagc atcccctgcg gtgctgacac cctctttccc 900
tgctctgccc cgtttaactg cccagtaagt gggagtcaca ggtctccagg caatgccgac 960
agctgccttg ttcttcatta ttaaagcact ggttcattca ctgaaaaaaa aaaaaaaaaa 1020
aaa 1023

<210> 149
<211> 1256
<212> DNA
<213> Homo sapiens

<400> 149
gctcagcctc ccaaagtgct ggtattacag atgtgagcca ccgcacccag cctgagtttc 60
tctttctctc tttttaactt tattttttga aaaacccggt agactttgtg gggagcattt 120
ttgttgataa tttactgatc taaagctgag tgattttta aaagaatttg aatctaatag 180
atctgtggtt gaatttsctg tgttgttatg aagtccaccc tgtgggcaca ataacataac 240
tgttggtagg agttgtttga gctattctgg agattatttg gtaaagtata ctaaaagcct 300
taaaaccatg tatgtgcgct gtttgaacca gtaagccact tctttgacat tagaagacat 360
tagaagaaat aatcagcctt gcataaaact tatggatgaa agtattcatc acaatattat 420
ttataataaa aaattgcaaa tgttataaat gaacaattgg gaaatggtta aagaagtgat 480
ggtgcattgt gtggtagaat attatgcata tgtttaaaga atcatatttt ctaagattat 540
ttggaagcat gtttggtaat gtcaagtgga gtaccccaga tacattttag acatttatcg 600
tcatcatctg ctctgagtgg aaggccgttc agagaggcta gaggttctta ttctggctat 660
aaattatgtg agtaaaattg tgctaaccag ttaaaagtac tgtacaccca tgctcaatat 720
atagtcctgg aaatagcaat tgaaacatgt cttctcacaa gagaaaatga cagttttaat 780
gatgtatttg atgaatttaa actttaagtc aggtgctgca aattggaaag aagacttgtg 840
gtgttttaag ttgctgtgga cacttttaag aaacttagaa cccatggaac ccttgtttat 900
cgccatgcaa attacaatct tgaatgagtg ttttttaaaa ataaagtatt agaaaaatgt 960

gtagtaaaga tgtaaaatta aaaaatggaa ttctccatta actgtggatt ttactaaata 1020
gaattactgg tgaagcagat ttatccatcg agactatctg gtatgcgtta tgtatgtagt 1080
ctgttgctgc tgaaagatgt ctgtgtgcct gtatcaacat gtgacttcat gtaaagtttc 1140
tttgtgttca cagttcttag caaatgcagt tacaatccat agatagccag cagtggatgt 1200
tactccagga aaatgcagga ttaaaattgt ccttgtgtaa aaaaaaaaaa aaaaaa 1256

<210> 150
<211> 698
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (683)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (692)
<223> n equals a,t,g, or c

<400> 150
cctcgctcaa gccctcagag aagaacattt tcaccctctt catggtggcc acagctgcca 60
tctgcatcct gctcaacytc gtggagytca tctacctggy ragcaagaga tgccacgagt 120
gcctggcagc aaggaaagct caagccatgt gcacaggtca tcacccccac ggtaccacct 180
cttcctgcaa acaagacgac ctcctttcgg gtgacctcat ctttctgggc tcagacagtc 240
atcctcctct cttaccagac cgcccccgag accatgtgaa gaaaaccatc ttgtgagggg 300
ctgcctggac tggtctggca ggttgggcct ggatggggag gctctagcat ctctcatagg 360
tgcaacctga gagtgggggа gctaagccat gaggtagggg caggcaagag agaggattca 420
gacgctctgg gagccagttc ctagtcctca actccagcca cctgccccag ctcgacggca 480
ctgggccagt tccccctctg ctctgcagct cggtttcctt ttctagaatg gaaatagtga 540
ggccaatgcc cagggttgga gggaggaggg cgttcataga agaacacaca tgcgggcacc 600
ttcatcgtgt gtggcccact gtcagaactt aataaaagtc aactcatttg ctggwaaaaa 660
aaaaaaaaaa aaaaaaaaac ccngggggggg gnccggta 698

<210> 151
<211> 1710
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (142)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (208)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (242)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (317)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1644)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1707)
<223> n equals a,t,g, or c

<400> 151
aatttcggcc cgagggtgag ggcagctgga gtgcgttctg ccgaagcttg tggttgcacg 60
cccttcgtct taggggctac cttccgtggt gagtgtgtgc ggtgttgcac ttggggttgc 120
ttctcgctgc gtggccgcac gnggctgaac ccttcccact ccatcccctc cccgcacccg 180
gaccagcccc tgggacgccc tcggacgncc acccgctcca accctgggga agcctcagag 240
tngcagcgaa ggcctyttgc ctttccgcct ctgcgcttgc tgtcatcgcc cacgtgcttt 300
gttgttgttc ggtgcanacc atgtccaagt ctctgaagaa gttggtggag gagagccggg 360
agaagaacca gcccgaggtg gacatgagtg accggggcat ctccaacatg ctggatgtca 420
acggcctctt taccttatcc catatcacac aactggtcct cagccataac aagctaacaa 480
tggtgccacc gaacatcgca gaactgaaga atttggaggt gctcaacttt tttaataacc 540
aaatcgagga gctgcccaca cagatcagta gccttcagaa actcaaacac ctgaaccttg 600
gcatgaacag gctgaacact ttgccacgag gcttcggctc cctgccagct cttgaggttc 660
tggacttgac ktacaacaac ttgagcgaaa attctcttcc tggaaacttc ttctacctga 720
ccaccctgcg tgcactctat ctaagtgaca acgattttga aatcctgccg ccagatattg 780
ggaagctcac aaagttgcag atactcagcc ttagggataa cgacctgatc tcgctgccta 840
aggaaatcgg ggagcttacc cagcttaaag agctccacat tcaggggaac cgcctcaccg 900
ttctgccccc agaactagga aacttggatt taactggcca gaagcaggta ttcaaagcag 960
agaacaatcc ctgggtgacc cccattgcag accagttcca gcttggcgtg tcccatgttt 1020
ttgagtatat ccgttctgag acatacaaat acctctacgg cagacacatg caggccaacc 1080
cagaaccacc gaagaagaat aatgacaaat cgaaaaagat cagccggaaa cccctggcag 1140
ccaagaacag ataaggaagg gattggcatc ggctggcctt ccagcacctt ctctctccaa 1200
cacttcattc tctcttgccc tgtctctcaa ataaacccaa tgctgcgtgt gaggcctttt 1260
ttatttttct tttcactctc tttctaatgc ttcccacctt accttttaga ttcttttgct 1320
aggtgggaga ttgttataag gtctttaaac catttccatt tgtttcttta acattaccaa 1380
aagcagggaa caaagctctt attcaactgc gaattccata gtgggctctg gcttttcttg 1440
aatagatatc acaaggttgc ttattatcaa aagaataatt aaaatcatgt aaccatttaa 1500
atgtcactgt taacactttt cactctttct gttgattcac ctaactcatt attttgcttt 1560
attaaaagtc ttccttcacc accgagatat gctaatttaa cttacaaatg attttaataa 1620
aatcttgagt ttgtaaaaaa aaanaaaaaa aactcgagag tacttctaga acggccgcgg 1680
ggccatcgat tttccaaccg ggtgggnacc 1710

<210> 152

<211> 1121
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (532)
<223> n equals a,t,g, or c

<400> 152
ggcacgaggc agaatggtcc tgccagccac agcagggccc tggtggggat ttgcactggg 60
cactccaatc ctggagagga tgccagggac ggggatgctg aggaagtcag agagcttggt 120
acggttgaag aaaactgagt cttgggcaat ttgtgctaaa actaggtgag ttgccaaacc 180
caaggcatct taccaacagc tggtttgggg gctggtttcc ctggtgttgt gtgttaccta 240
ccctttggct tggcttgacc tctccttgtg agctcacctg agccctccca gggccaggtt 300
cctgacagtg ttggtttttg cacatccact ggaaaggtgt cattaatgac ccagtgttag 360
aatgcaagag gtcaggttat tctagccctc atggctgaag gcccagtcct ggctccacca 420
ctcctccagc cagagggtct ggaccatcca gtgcctgtcc tcgccacagg gcctccaggg 480
agcattcggg tcaawtccat ggacaccctg ggctacaaac caaggctgct gntcatccca 540
catcgtgtgg ggcagtgtcc atcccctgca gctacttggt gacttaacaa ctycaggagc 600
cctgtcagct gccctcctcc acctaaaccc cttcgactct tctgctttga caaagaaaat 660
gacattgggg aggggaggtg ctccgcctcc cagcttttct caaaatagtc ctatagatac 720
tggtaatctg gaaatgaaga agtaattctg tctctgcacc tacttttgca gaatgttcaa 780
ggaagtattc tgtgttagta ttaatgccaa aaagttgttt ttaaaggttt tgtactcagc 840
acatcataca aaccacatta cttctgtcac ttcagggcat cgggactggc tggcgccctt 900
gttatgtgct attttaatca gtgtaacatt ggtcaagttg ttacccatgt atgctgtgtt 960
tatcatgtgt atatcgtcya gaaagtatta aggctttagg tagatgcaac tggcgaacct 1020
tggagaggga atgctgattg tcttgaccaa acccacagcc tgtctcttct cttgtttagt 1080
tacttacggc aataaatcat ctatgagtta gtgcaccgtg a 1121

<210> 153
<211> 445
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (440)
<223> n equals a,t,g, or c

<400> 153
ttttcttgca tctgcccgcg atcttctccc agacctttct gcgagtacga gccaaccggc 60
agacccgact gaatgctcgg attgggaaaa tgaaacggag gaagcaagat gaagggcaga 120
gggaaggctc ctgcatggct gaggatgatg ctgtggacat cgagcatgag aacaacaacc 180
gctttgagga gtatgagtgg tgtggacaga agcggatacg ggccaccact ctcctggaag 240
gtggytttccg aggctctggc ttcatcatgt gcagcggcaa agagaacccg gacagtgatg 300
ctgacttgga tgtggatggg gatgacactc tggagtatgg ggaagccaca atacacagag 360
gctgatgttc atcccctgca caggcgagga gctggttgaa gccaaggaga gagaggcatt 420
tcggggcgca ttcttaaatn gccgg 445

<210> 154

<211> 798
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (638)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (665)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (698)
<223> n equals a,t,g, or c

<400> 154
agctcttaga caggtacaga gaactacaac ttagtacaga aagcaaagta acagaatttc 60
tccatcaaag taaattaaaa tcttttgaaa gtgagcgtgt tcaacttctg caagaggaaa 120
cagcaagaaa tctcacacag tgtcaattgg aatgtgaaaa atatcagaaa aaattggagg 180
ttttaaccaa agaattttat rgtctccaag cctcttctga aaaacgcatt actgaacttc 240
aagcacagaa ctcagagcat caagcaaggc tagacattta tgagaaactg gaaaaagagc 300
ttgatgaaat aataatgcaa actgcagaaa ttgaaaatga agatgaggct gaaagggttc 360
tttttcccta cggctatggt gctaatgttc ccacaacagc caaaagacga ctaaagcaaa 420
gtgttcactt ggcaagaaga gtgcttcaat tagaaaaaca aaactcgctg attttaaaag 480
atctggaaca tcgaaaggac caagtaacac agctttcacm agagcttgac agagccaatt 540
cgctattaaa ccagactcaa cagccttaca ggtatctcat tgaatcagtg cgtcagagag 600
attctaagat tgattcactg acggaatcta ttgcacanct tggagaaagg atgtcagcaa 660
cttanaataa agaaaagtca gctttactac agacggangg aatcaaaatg gcattaggat 720
ttaggaccaa cttctaaatc atccgtgaag gaaatttggc aagcaaatga aaaccagatt 780
cctcggttaa gatgcatt 798

<210> 155
<211> 400
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (74)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (379)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (383)
<223> n equals a,t,g, or c

<400> 155
ggaatctgga agcctgactt tgcccccagg gaagttgggg accgccttcc ctcccttctc 60
cacctctcac tctnggcacc ctctccaatt gcactaaagt agctgttgtg ccagtctgcc 120
ccccacaagg ggggaggtct ctgcttycag tcttcttccc ccgctgcctc cgctmccacc 180
ctggacaatc tccttgtttc ccttgtgttc mtggayagct cagctttgta tgtgtgtttg 240
gggggtgggg gtgggttctg gcttgagtgg gtttggcagg ggtttgggaa gggttagggg 300
aggatggagg atgaagtctc ctaccccctt ctccagctcc aggccacaga agcctgggaa 360
agggagggtg cctactctng gtngctagtg tgtctttgca 400

<210> 156
<211> 1757
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (596)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (647)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (648)
<223> n equals a,t,g, or c

<400> 156
gccagccacc attttatctc tctaaagtct ggtcccagta ttaaacctat tctttagtaa 60
actcatatta ctgttctaaa ttgaagaaat tatttattac tctgtacttc tagactcaaa 120
attctttatc aaagatagtc tcaaagaggt agtacaagtc ctgtttaact gcactttttc 180
acattcacag tgcttcctct gatatctttc cttacatcat tatacactgt tgatatcatt 240
ttactcttct ttctcttcta catttcttaa attttggttc ttttcctgta catgtgtttt 300
agcggggccc ttttctttga actttgtcta attagcctgt acatttttgt ttcttttaag 360
gtagaacaga tcttttttttg tttctccttt taagtctact ggttttaaaa gaggtaaatg 420
tatccataga ccacagtgcc ttgctttttc ctctgccagc acatggagca cgggattaga 480
tgcacaaacc tatttaggga actattttgg tagatgtttg agtttataca gaaattgcag 540
ctggtatttt attttgctgt acatttactc aacttgtcca ttagtattta actatntcca 600
gagtttgttt aggagtaaga attgacccat tcgttagttt accatanntt ttcctggtat 660
aaaaaggagc cagaaataag ccttattgct aaataattaa ttatgtaagc ccacctaggt 720
cctgcataag atccccctca catacttcac aatatatatg tgtgtgtgtg tgtgtgtgtg 780
tgtgtgtgtg tgtgtgtgtg tgtgtatktg gctaaaaaat tatactgcca aaattactga 840
ttataaatac ttgactacac tgattgatgg gacaaaatga ttaaagtatt ttcagggatc 900
ttattccata tgtcaccacc aaagatttct acagtgttat aaagtatata aatattccaa 960
atttctgtgg ttaaatattt ttttcttttt tttccttttt tagaataaca cagtctgtgc 1020

tttccaaaaa tgcttgaact tttatgttgt taagaaatat ataatgatat cttacattaa 1080
gcatgagtct aatttgtatt aattgggatg gactaaattt tcatttgatt atcaggaaaa 1140
ttaaggagtt atatatttaa aagcaatttt ctgtgttttc ttctttgtaa gttgactcat 1200
ttgtgaagca attaggcaaa ttttgagaag atcattgtta ttgtggtttg cagtatatat 1260
ttcttagtaa atatcactta agattaaatt tttcagaaag aaaattatag ctttttttccc 1320
aaaatatttt taagatttaa tctttttgta gtatgctaca gatttaatta tattaactct 1380
tttttaagac attgaccatg acttaacatt ttgccttcta acacctttta aatctatgta 1440
ctttaatagt taagagaaaa taagtttgca gatttttaat aatctgtttg taaaaggcta 1500
tctctaagcc tagtatgtgg gtaattttac aggtgtgttt tttgataact ttaatataaa 1560
ataaactcat tttatttgtg gcaattcgcg tttctttttt tatgccagag tacatatgtt 1620
ggattccatg aattggtatt acttattatt atgtgttgat taaatatatg cacacactta 1680
ggattacaga tcacagagca aattatgaaa atcataaaca ttctggtatg gtcatccata 1740
ggattatgaa aaagaaa 1757

<210> 157
<211> 1245
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1245)
<223> n equals a,t,g, or c

<400> 157
gaaagccctg aatgttgtac aaagtgtttt gcaaatcaac ttaagcaatt ctacaaacag 60
aggatcagta gctgctaaga aatttaagga catcatacat tatgatccaa cgaagcaaga 120
ccatgccact tacgaaagaa aaagagatga taagccaaaa gaaagtaaag caaaacgaaa 180
aaagaaaagg gaggaagctg agaaactacc tgaggtgtct aaagaaatgt attataatat 240
tgctatggat ctgaaagaaa tattccaaac tacaaaatat accagtgaaa aggaagaggg 300
cacaccctgg aatgaggact gtggtaaaga gaaacctgag gaaatccagg accctgcagc 360
tctgaccagt gacgctgagc agcccagcgg gttcacgttc tctttttttg attcagacac 420
taaagacata aaggaagaga cctacagagt tgaaacagtg aaacctggaa agattgtctg 480
gcaggaagac cctcgtttac aagacagcag ttcagaagar gaagatgtta ctgaagaaac 540
agatcacaga aactccagtc ctggagaagc atcattactt gagaaagaga ccactagatt 600
tttctttttc tctaagaatg atgaacgact tcaaggttct gacttattct ggagaggagt 660
aggaagtaat atgagcagga actcttggga ggccagaaca accaacctgc gtatggattg 720
tcgaaagaaa cataaagacg caaaaaggaa aatgaaacca aaataataaa tgtcagctgg 780
ttttgatact gaatgtgaac aaggctcacc taaggaaact gacccagaaa acagttttag 840
ctgacaaaga agaaatttca gagtgaagga attttaaaaa tctggctgac ggaatatcat 900
tctggttgcc atctttttct gtggaactcc tctgcatttc ttcctaagta attacttcaa 960
aaattaaatt caacttctta taaaggaaga acaagatagt ccttgaaaat actttttgta 1020
tataatctct ttgccctcta tcctgagtaa ctaatggaca tcttctcatg caaggtttay 1080
atgaagcctt tttwaataaa tgagtcaaag cacttgtatt ttccagccta ggctttgtgt 1140
gaattatagg ctatttgaaa ttttatttct gattatgtca aatacacctt ccgattttgt 1200
catttttgtt taaactgata aattacaagt caacattgag ttttn 1245

<210> 158
<211> 379
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (375)
<223> n equals a,t,g, or c

<400> 158
gtgagctgag accatgccac tgtactccag cctgggcaat agagcgagat tctgtctccc 60
aaaaaaaaca aaaaacaaca acaaaacttg ctaccaccca gggattttct gctatttaaa 120
aggtgaattt cttttctggt actaaactgt agctgcttaa cttagtaaag gctgtgtttg 180
gccaggcctg tgccagaggt cacctggagt gctccaccca ctggcaggca agtcctattc 240
ctattcaccc aggatcccca aggctgggct gggatataaa tgttgggata ggaaagaaat 300
atttcctttt tagaggaaag caagaagaaa cattgcctga aagtgattty ctagtcattt 360
ccattagtac agaangtta 379

<210> 159
<211> 474
<212> DNA
<213> Homo sapiens

<400> 159
ctttatcata ttttacaaat gtgtgagtct gctatggatt agaaattaat aagagatttk 60
gccacagata gtttgagaag cccagcactg ccactcaaca aatgctggtg cattcagatg 120
gtgaaatatt ctgcagctat taaaggagtt aaaactgcct ccacttacct ggaggcccat 180
ctgtgacacc tttttaggtt aaaaggaaaa gaaaaacttg cttaggactg aatatgagcg 240
gttgcaattt gtaacaatga tgtatatata catatacatt ttcatgtatt tgtatgaaca 300
taaaagtatt gaaggatatt catcaaactg ctaaaagggt tgcttcagag taacggactc 360
ggagaaggca gattaatttt ctcttaatgg aactctgtat tgtatcactt gtaaaaataa 420
gcatgtgtta tctttatgat aaaaaagtaa aaacctaaaa aaraaaaaaa aaac 474

<210> 160
<211> 1444
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (4)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (5)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1373)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (1425)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1430)
<223> n equals a,t,g, or c

<400> 160
gggnntagac accttagaga ttcagcagca agccctgcta agagagcagc agaagaggct 60
gaacagaata aaaatgcagg aaggtgccaa agttgactta gatgccatcc caagtgctaa 120
agtacgagag caaagaatgc ccagagatga cactagtgat ttcttgaaaa actcattatt 180
ggaatctgat agtgctttta ttggggctta cggtgagaca tatcctgcca ttgaagatga 240
cgtcctccct ccaccatcac agttgccctc tgcacgggag cgcaggagga acaaatggaa 300
aggactagac attgatagca gtcgtcctaa tgtagcacca gatggtctct ctctaaaatc 360
tatatccagt gtaaatgttg atgagcttag agtgagaaat gaggaacgaa tgcgaagact 420
gaatgaattt cacaataaac ctattaatac agatgatgag agttcactgg ttgaccctga 480
tgacatcatg aaacacatag gggatgacgg atcaaactct gtagcaactg agccctggct 540
ccgccctggc acttcagaaa cgctgaaacg tttcatggca gagcagctga accaggagca 600
gcagcagatt cctggaaaac caggcacttt cacttggcag ggcctgtcga ctgcacatgg 660
ttaaaataaa cctgtactgg acccagtagt gccttttaag gtgaaaggaa tggtaaatct 720
gtacctttaa tatgtcctac ttttggcccc tacctgaaag ttactttttt tccatcatct 780
gtatataaaa ttatttttat catgatgtat attatgtaca taaataaaag gccatgatta 840
ttgatttata taatagaatt gtatagatta tttttgcaca gttttgtcat aaattagggt 900
ggtaatgaac tggattgaac tactatatgt gcattatatt gaattctgct tgtcattaag 960
ataaggtgaa taagtgtctt aaacgtcctg taaaaccgga ctcccctttg ttacatgcac 1020
attttccatt gttacctcga tgcaaaagaa ttcatttagt aggtacatct attgtagctg 1080
tgattattcc agtttctgtg tgatgcaatc aaatgtccta ttaattaatt attatttcat 1140
gtcatttgta gctactgata cagcagaaat gaagggaact gtaattactt gtatttttgt 1200
aagccatacg ttaaatgttt gttacatcat ctttctgctt ctatttttat gccaatgaag 1260
gcatttgtct tgttactaat tacatgatgt aactacttct tgatataaat aaatttttat 1320
tttaattact aaaatctttt taactactat ggagctttct agactagttt tcnagagggt 1380
gaatagaggt ggggacaccc ggggagtcaa ggacagagga gactnggagn cttccttctt 1440
ccca 1444

<210> 161
<211> 449
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (268)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (269)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (368)
<223> n equals a,t,g, or c

<400> 161
aattcggcac gagttggaat gtgagatggt ggttgagagt caggatctct tttaaaagtg 60
atcttgagca agttatttaa actttctaat tatcagtttc tttatctgta aaatggaggt 120
aatgggaata cttacctcaa attgctgaga gaattaaatg aaataattct gcaagatagt 180
tatcacagta aagcagtaaa tgctccattc agggtaccat tactattgac tgccttaaaa 240
atttaatctt ctagccaggt gcgaaaannc atgcttgtaa tctcaacact tttggaggcc 300
gaggtgagat gatcatcttg agcccgagag ttcaaggatt aaccagagta acatagcagg 360
gatcttgnct ctattttttt aaaaaagtca ccttgtaaca ctggtgaatt ggataaggag 420
caattcagat gtagcgaatt ttaataatg 449

<210> 162
<211> 573
<212> DNA
<213> Homo sapiens

<400> 162
cccaccctga aagccctgag ctttctgcta tcaaagaggt tttaaaaaaa tcccatttaa 60
aaaaaatccc ttacctcggt gccttcctct ttttatttag ttccttgagt tgattcagct 120
ctgcaagaat tgaagcagga ctaaatgtct agttgtaaca ccatgattaa ccacttcagc 180
tgacttttct gtccgagctt tgaaaattca gtggtgttag tggttaccca gttagctctc 240
aagttatcag ggtattccag agtggggata tgatttaaat cagccgtgta accatggacc 300
caaaatttac cagaccacaa aacttttcta atactctacc ctcttagaaa aaccaccacc 360
atcaccagac aggtgcgaaa ggatgaaagt gaccatgttt tgtttacggt tttccaggtt 420
taagctgtta ctgtcttcag taagccgtga ttttcattgc tgggcttgtc tgtagatttt 480
aggacccwat gctgcttgag rcaactcatc ttagggtggc aaaaaggcag grtggccggg 540
cgcgtggtca mgsctgtaat cctagcactt ggg 573

<210> 163
<211> 1037
<212> DNA
<213> Homo sapiens

<400> 163
aattcggcac gagctgtctg cgaagtggcc cttgattaca aaaagaagaa acacacctaa 60
acactttatc tccaagttac aaaagtttga ggtgcagagg gaaggccaga tttttttttt 120
aatgaaatta tatagattag atctcagtat ttaaactgtt cctcaatttt gtgaggctgt 180
gttggaaata acccgcctct agtgctgttg gtatgcaagg cagcggtgct taatcaatat 240
ttcctgtgct caccagaggc aaaatgtacc aatatcctga caccattctc tctccattta 300
cttctggtgg ttaccctgac tcttgactct tagaagtgcc cgagatgggg ctaaccttta 360
ttaaacagat cgcatattat gatcttgctg cagccacagt gcagctccac attaactcta 420
cagaccaaac catttgtatc tggcatcact tactaacaca cgacatgcgg cttttctgca 480
tcaactgcta tgacggttaa gaatgtcagt atacaagaag gaatagaaaa ctgatactgt 540
tttaaataat ctgtaatttc aatttttttt ttttttgct gaaatacatt atattgtacg 600
tttgagataa ttctagtaca aagtataata aaactagatg tataataaac cctttaaatc 660
attggtaagt gtacaagtgg tggaactgaa gcatttactg gacaaagtaa tgttactcta 720
atggttactt gctcgtgcgt tgccacactg tgttataatt tgcttcattt ccttgctatt 780

tgatacatag tgtgcatttc tctgtcactg taactattgt aatgacaaat tttcatctta 840
ctgcacaatc aaaatgacat tgataggaat gaactccaga ggctgggcct gaacagggag 900
gtggtcgctc aggcctggtg ctcagtcgta cgacctgtac ctctcaactt ttgccctatc 960
tgttaaatat atgctatgtc attaaatgct tttaaatcta aaaaaaaaaa aaaaaaaaaa 1020
aacggggggg ggcccgg 1037

<210> 164
<211> 921
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (881)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (908)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (913)
<223> n equals a,t,g, or c

<400> 164
cccccccccc ccttgtggac agctgtgtta ataaggccaa ttttctgaga atgtgggaaa 60
gattaaaata tttaactgtt tatctttcac agagtagcag tagctctgat taagcctata 120
ggcaattaaa agtagtttgt ctgtaaaaag agggaaagaa ataagatttc ttaccccatt 180
ttatggactt ttaaaaatta aaaaactgcg cccccgccca ggagctcttt tcttatgaca 240
tataaattat gacatttata ttctttatat gactttatgt tctcttctta tgacatttaa 300
attctttaag tagtttgttg gtccaataaa ctagacgttg tataatctaa attgagccct 360
tgtatatcta aaactgatga gttgtttcta aattgttgat tgtccattta cttgcctttg 420
gtattaagat aatgcaagta aagtttagta agtcattgga taatgaaatg attatgtttc 480
tgaagaccat attatatttt taatttttag aggaatcatg ccatccccca aaaaatcaag 540
aaatatttga attttaaatt ataagttcat ttgttaaaag acatttttac aaatgtctga 600
aaatcttaaa atactttaca tctaccttta agtagtagaa tacagagctg taaatttcca 660
tgcctttttt cctgatatta agttttatag taaaaaagca actagtgatt gcacaaagaa 720
tataaaaatc caytcttttt acaaaggtgt gaatttaaat aacgttattg attggaatat 780
gaaaataaac caatcattta agagcttttt agcaaatgat ccaattctta ctccttttct 840
cccaagattg gaaaagcata atgtttttcc tcctaaagtt nggaatccta gaaaagcccc 900
ggtgagtngg acnaatgttc c 921

<210> 165
<211> 465
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature

<222> (428)
<223> n equals a,t,g, or c

<400> 165
aattcggcct cacagagatc atcatcttta ccaccttcaa atcgtaaatc aagtactcca 60
aaaaaaactt attctgagaa agccaccgat aaccatgtta atcatagctc ttgccctgaa 120
ccggtgccaa atggagtgaa gaaagtatct gtgagaacag cctgggagaa gaataaatca 180
gttagctatg aacagtgtaa gccggtttca gtcactccac aggggaatga ttttgaatat 240
acagcaaaaa ttcggaccct agctgaaaca gaacgatttt ttgatgaact tacaaaagaa 300
aaggaccaga ttgaggcagc actaagcagg atgccttctc ctggaggacg ratcacttta 360
cagamraggt taaatcagga agccttggaa gatcgtttgg aaggattaat cgagaactgg 420
ggttcagntc gcatgacgct aaagaattcc atgttttgcg cacct 465

<210> 166
<211> 752
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (651)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (662)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (684)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (693)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (700)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (711)
<223> n equals a,t,g, or c

<400> 166
gtggaaactt tttccatcct gttttctctg ctatatctgt cagcccccat ytccaccwac 60
atcagagaag acagcatcgt gaagcttctg tggcagcctc ctaaggaagg ggctgccaat 120

ctgtagttgg cagatgctat aggaattgct tacaaatgtc gtctttaaga aaaatgttct 180
tatattttc ctatgggcaa aatgaaggct tgggtgctca tctaaagctc agccaactcc 240
tgaagcactc tctcagagca tactgctgct gtaatgggct ggcttaatta tcggcagagt 300
gcttgaaaag gctttgcaga cctcccctgc ccccaagact gggtgacttt atatgtactt 360
cattcaaggg taaatcaggg agacgttctc catttatctc ttcgtccttc ctgcctggga 420
aagtgatagc actaaatatt tcccagcagg atggggtagt gtttctcaaa ggaatcaccc 480
tttccctacc ttcagactca ttctttaccc ttccattgst ccagtgctga tggaggccaa 540
agacaacccc agggttttca taggaaattc actggaattg tgcgcaattg tctttgtagt 600
ccttttgcct tttttttttt taaatattta tgttggcaat agcatttgtt ngggtatttt 660
gntttaaaag gcctcactct aagntattac cgncccсttn attggttttt naaagacatg 720
tggggggata tagtttttaa aaaataaacg ta 752

<210> 167
<211> 1631
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (255)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1620)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1630)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1631)
<223> n equals a,t,g, or c

<400> 167
tccagagatg tttcctgtcc tccccggttc ccacttgctg ytcaataacc ctgccctgga 60
gttcatcaaa tacgtgtgca aggtgctgtm cctggacacc aacatcacaa accaggtgaa 120
taagctgaac cgagacctgc ttcgcctggt ggatgtcggc gagttctccg aggaggccca 180
gttccgagac ccctgccgct cctacgtgct tcctgaggtc atctgccgca gctgtaactt 240
ctgccgcgac ctggnacctg tgtaaagact cttccttctc agaggatggg gcggtcctgc 300
ctcagtggct ctgctccaac tgtcaggcgc cctacgactc ctctgccatc gagatgacgc 360
tggtggaagt tctacagaag aagctgatgg ccttcaccct gcaggacctg gtctgcctga 420
agtgccgcgg ggtgaaggag accagcatgc ctgtgtactg cagctgcgcg ggagacttcg 480
ccctsaccat ccacacccag gtcttcatgg aacagatcgg aatattccgg aacattgccc 540
agcactacgg catgtcgtac ctcctggaga ccctggagtg gctgctgcag aagaacccac 600
agctgggcca ttagccagcc ccgggccccg ggtgcctctg cgtccgtgcc aggcctcctg 660
atgccaaggc cacatccccg tgcttccagt gaccagacca ctgaccaccc tgactgtcca 720
aacctgtgac cccaggccag ggaacgggga ggaaaccaaa gaaaaccatt ttcagggagc 780

tcagacgtca caggagggag cgggagcagg atgtggccct ggcctcgcca gagcacctga 840
agaagcaggc cgtgagcgag gctgcgagtg ccctgggcgc cgtttctcac gcatgaatgc 900
ttttccaggc ctctgttgct tcctgcacca cacctggtgg ggtgggagcg tcctctagtg 960
cccctagttc tttgtcctgc ctcccagagg gaggaaaaag cccctggggg cttctggctc 1020
cctgagattg ggctctgaga cgagacgggt tcccaaggcc ctggtggggc tggagtctca 1080
cctgtttgca tggagaaatg ggctggcccc acagcctcac aggagcagtt tgtgggctgg 1140
tttccccrgg aatccagacc ctaacccgtg agaatctgga ttttggcttg tgagccctgc 1200
ttatttggag ccgggtctag agggaaccct ctatcagcct caggaaaaca agacctctgt 1260
gcacctcact tttggctcac tgcagccctt gtccttcacc tccacacagg accagctgga 1320
agcagaaaga agaaaggcca atttcacagg gcaccaaaca agtatgaaat gtaaatcaga 1380
aatgcagaca ccccagacga gagcctcaca ggagggaggg ggccccacag gctccccagg 1440
aggctcgtgt ctttggccca gagccagcct tagtttgtcc ctgccatcta ctgtctgagg 1500
ccatcgctgc tacactttgt ttttatttgt atttcatact gaagtttcaa maaaaaaaaa 1560
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaan 1620
aaaaaaaaan n 1631

<210> 168
<211> 740
<212> DNA
<213> Homo sapiens

<400> 168
tttttgaatc ggttgtggcg gccgcggcga ggaatggcgg tatttgtgag aggagtcggc 60
gtttgaagag gtggaactcc tagggctttt ttgagagtgc tgatttagaa gaatacaaat 120
catggctgaa aatagtgtat taacatccac tactgggagg actagcttgg cagactcttc 180
catttttgat tctaaagtta ctgagatttc caaggaaaac ttacttattg gatctacttc 240
atatgtagaa gaagagatgc ctcagattga aacaagagtg atattggttc aagaagctgg 300
aaaacaagaa gaacttataa aagccttaaa ggacattaaa gtgggctttg taaagatgga 360
gtcagtggaa gaatttgaag gtttggattc tccggaattt gaaatgtatt tgtagtcacg 420
gactttcagg attctgtctt taatgacctc tacaaggctg attgtagagt tattggacca 480
ccagttgtat taaattgttc acaaaaagga gagcctttgc cattttcatg tcgcccgttg 540
tattgtacaa gtatgatgaa tctagtacta tgctttactg gatttaggaa aaaagaagaa 600
ctagtcaggt tggtgacatt ggtccatcac awgggtggag ttattcgaaa agactttaat 660
tcaaaagkta cmcatttggt ggcaattgta cacaaggaga aaattcaggg ttgctgtgag 720
tctaggtact ccattatgag 740

<210> 169
<211> 2038
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1490)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1508)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1979)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1992)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2010)
<223> n equals a,t,g, or c

<400> 169
tcgacccacg acgtccggcg gcgggaagct ggcggcagcg gtcggtggcg gtggctgagc 60
agaggacccg gcgggcggcc tcgcgggtca ggacacaatg tttgcacgag gactgaagag 120
gaaatgtgtt ggccacgagg aagacgtgga gggagccctg gccggcttga agacagtgtc 180
ctcatacagc ctgcagcggc agtcgctcct ggacatgtct ctggtgaagt tgcagctttg 240
ccacatgctt gtggagccca atctgtgccg ctcagtcctc attgccaaca cggtccggca 300
gatccaagag gagatgacgc aggatgggac gtggcgcaca gtggcacccc aggctgcaga 360
gcgggcgccg ytcgaccgct tggtctccac ggagatcctg tgccgtgcag cgtgggggca 420
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cctttgccca gtcacctcag cacaggcacc aaggcacctg cagagcagcg cctgggagat 540
ggatggccct cgagaaaaca gaggaagctt tcacaagtca cttgatcaga tatttgaaac 600
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<210> 170
<211> 522
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (471)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (488)
<223> n equals a,t,g, or c

<400> 170
ggcacgaggt taatctaagg tgaagcaaac agaaaattgt ggaggttttg ttggtgtgca 60
actgaggaac atggctcaag aaactaatca cagccaagtg cctatgcttt gttccactgg 120
ctgtggattt tatggaaacc ctcgtacaaa tggcatgtgt tcagtatgct ataaagaaca 180
tcttcaaaga cagaatagta gtaatggtag aataagccca cctgcaacct ctgtcagtag 240
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agaatctgta gcatcttctc aattggacag tacatctgtg gacaaagcag tacctgaaac 420
agaagatgtg caggcttcag tatcagacac agcacagcag ccatctgaag ngcaaagcaa 480
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<210> 171
<211> 1666
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (114)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1659)
<223> n equals a,t,g, or c

<400> 171
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gaccgcatct ccccccacgg ggtcggtgcc tggggatcct gtccgcatcc actgcaacat 180
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agatgaagat gaggagatgc ctgaggacac agaagactta gatcactatg aaatgaaaga 480
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catcctagag aaaattaaaa agaaccagag gcaagattac ttaaatggtg cagtgtctgg 600
ctcggtgcag gccactgacc ggctgatgaa ggagctcagg gatatatacc gatcacagag 660
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caaactcctc aaagttgacc aggacagcgc tttgcacaac gatctccaga tcctcaaaga 780
gaaagaagga gccgacttca ttctacttaa cttttccttt aaagataact ttccctttga 840
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<210> 172
<211> 438
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (413)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (438)
<223> n equals a,t,g, or c

<400> 172
gcggaggagg tgtatgccca gctgcaaaaa atgcttctgg agcaacaaga gaagtgcctg 60
ctgttctcca agcagttcat gcaccagggc aacgtggctg agaccacccg atttgagaag 120
cttgctcagg accgcaagaa acagctggag atcctgcagc tggcccaggc tcagggcctc 180
maccctccca cccaccactt tgagttgaag acattccasa ctgtgaggat cttctcacaa 240
ctcaacagca cagaaatgca tctgatcatt gtccggggaa tgaacctccc agcccctcca 300
ggggtgactc ccgatgacct ggatgctttt gtgcggtttg agtttcacta ccctgactcg 360
gaccaagctc aaaaaagcaa aacagctgtg gtgaacaaca caaactctcc cantttgatc 420
actcttcaac taaactcn 438

<210> 173
<211> 2511
<212> DNA
<213> Homo sapiens

<220>

<221> misc feature
<222> (12)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (28)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (44)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2456)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2488)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2511)
<223> n equals a,t,g, or c

<400> 173
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gccagattcg gccgagcaag cggaacctct gggaaaagca atctgtggat aaggtcactt 120
cccccactaa ggtttgagac agttccagaa agaacccaag ctcaagacgc aggacgagct 180
cagttgtaga gggctaattc gctctgtttt gtatttatgt tgatttacta aattgggttc 240
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tcacagtcta gagatgttca tggtaaaagt actgcctttg cacaggagcc tgtttctaaa 360
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gtgataccaa ccacatctga agtcaacaga agatccaagt ttaaaattgc ctgcggaatg 480
tgtgcagtat ctagaaaaat gaaccgtagt ttttgttttt ttaaatacag aagtcatgtt 540
gtttctgcac tttataataa agcatggaag aaattatctt agtaggcaat tgtaacactt 600
tttgaaagta acccatttca gatttgaaat actgcaataa tggttgtctt taaaaaaaaa 660
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attattatgt tagctgacag tggtactgat tttttaggtt ggttgttttg tggatttctt 780
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cacatataca aacacactaa tggtagaatg ctttttttatg tgctagacta ttatatttag 900
tagtatgtca ttgtaactag ccaatatcac agcttttgaa aaattaaaaa atcacactat 960
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cctgatgacc tataagaaga aagtattgaa aagaagagag attagaactg ttagaaggag 1080
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gaagttcaca ataggtcata aggtctcttc cttttctaaa attgaaagac aagaaattta 1260

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<210> 174
<211> 230
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (4)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (19)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (227)
<223> n equals a,t,g, or c

<400> 174
tccntcccag tggtacttnt actaaattgt tgtcttgttt ttatttttta aataaactga 60
caaatgacaa aatggtgagc ttatgatgtt tacataaaag ttctataagc tgtgtataca 120
gtttttttatg taaaatatta aaagactatg atgatgacat ttaaaaaaaa aaaaaaaaaa 180
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaanggg 230

<210> 175
<211> 1191
<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (44)
<223> n equals a,t,g, or c

<400> 175
ggcagagcgg cacgagatgt gagccaccat gcctgggtgt ctcnttcatt ctttaggcag 60
ttcattgtca cttccttcca ttggtaaaca tgtaaattat agtcgcatga tttagaattt 120
tactgaccaa agtcataata atagttaaca gtacaaggaa ctattttkgt ataatggttt 180
atttaataca gtatacatta tctttcatat actttgttac aatgttaaaa aaacttcatt 240
tttcataata taggaaataa agttggaaac aactctggtg ggaatacttc agatagagca 300
agaaagcatt cacagcaagg cctataatca gtaagatgtg tgaaaagttg ggtagccaca 360
ggaggtgttc attaaggata tgattccatt tatatagcta tttctattgc ataaccagga 420
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ttttggccca gaaagcctta cttattttac awcttccagt ttgtccatcc catgagttag 540
agttcgtctt gactctgcaa gctagaatca aagaattatg aaagtaagat catttagatt 600
tgaccaaggg caccattaaa tggtgtcagg ttttaggaag cagacgggtg tataaaaaga 660
aaatgaacaa agatttcact tattggggat caggcataac tggatgcctg gattgtcctg 720
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<210> 176
<211> 1499
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1462)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1476)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1495)
<223> n equals a,t,g, or c

<400> 176
gccttctccc gcctccctcg gccttagcca tggcgagtag cggcggtgct ggggcggcgg 60

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atgacaagct gactttctgg agaaattctg atgagatatg tcaagctctg caagrgggtt 180
tgaagattgc attgtagttg agaatgtaca wtgaaattwc tgcatgcagc agtgtagaaa 240
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cattattctt gcctttaaaa ttttaactca tcaaagtgaa gattagaaat aaattttagg 1380
aaaatgtagg aatagtattg attctgtccc tgtaatagga atctcagtgg ggtttttttg 1440
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<210> 177
<211> 1538
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (50)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (727)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1218)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1487)
<223> n equals a,t,g, or c

<400> 177

tgtaccggga cctgcagccc gtgggctcgg gcgcctacgg cgcggtgtgn tcgtccgtgg 60
acggcgcacc gscgctaagg tggccatcaa gaakctgtat cgkcccttcc agtccgagct 120
gttcgccaag cgcgcctacc gcgagctgcg cctgctcaag cacatgcgcc acgagaacgt 180
gatcggkctg ctggacgtat tcactcctga tgagaccctg gatgacttca cggactttta 240
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cgaggaccgg atccagttcc tcgtgtacca gatgstgaag gggytgaggt atatccacgc 360
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gctgaagatc ctggacttcg gcctggccag gcaggcagac agtgagatga ctgggtacgt 480
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caagggcagc gaccacctgg accagctgaa ggagatcatg aaggtgacgg ggacgcctcc 660
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<210> 178
<211> 896
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (194)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (825)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (828)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (831)
<223> n equals a,t,g, or c

<400> 178
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caggatggga tagctcggct ggtgggtgag gggggccatt tgtttctcta ttacacagtg 480
gaaaactccc gtgtgtatca tctggaagaa cccaagtgct tggaaatata cccccagcaa 540
gctgatgcca tggaactgtt gcttggttct tatccagagt ttgtgagagt gggggacctg 600
ccctgtgaca gtgtggagga ccagctgtcc ttggcaacca cgttgtatga taaggggctg 660
ctgctcacta agatgcctct agccctaaat tagtttcttg ttgattgctg gaaacaaggc 720
agtagtgatt ctccgctgcc actgctaact tttttttttt tttttttttc cttaaactca 780
agttcttacc ttgataagca tcagtgtgct cacatttacc tttancantg ntcagtgtca 840
caaacctcgg aaggtctcta ggaagaacca tctcatctag gtacaaaagg gaaagg 896

<210> 179
<211> 568
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (67)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (469)
<223> n equals a,t,g, or c

<400> 179
ttatcttaga tttctagtta tttatatatt aactttttgt ttattcagaa tcattttcct 60
gtttgtngga atatttctaa gagccttggg aaaatctcga gtaaaatttt aaatgaaatt 120
tgtatagtgt tctgcctctt tccaaaggta tttctcaaaa ttgggaattg ttttattatt 180
gaagttgaat gacttcaggg gaactctaaa atgcaagatg ggaagcttct gtttggtttt 240
ttcctttccc tttggtaagg tcttttgctt cccatcccct tgacccacct ttgtgctgtc 300
tgttgtccag tctgctctcc kgatccctaa rgakgtttct tatctaggct gccatttatg 360
tgggtaaaag acaaggtaga aaatactctt ctgtatcttg tatcaagggt taatctaatg 420
tcttcatcac tttgttttga ratattttgg aatgttatcm acaattatna tagatggagc 480
atgtatgtct taggtttggt gttaatgttt aacatgcatt atcttattca atcctcacag 540
cagtcataaa atgtaggtgt tttagagg 568

<210> 180
<211> 428
<212> DNA
<213> Homo sapiens

<220>

<221> misc feature
<222> (405)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (413)
<223> n equals a,t,g, or c

<400> 180
aaacacctat ggaaataatt ttgttttttt tttttaaaa aggaatgaga tcatgtcctt 60
tgcagggaca tggatgaagc tggaaccatt atcctcagca aactaacaga ggagcaggaa 120
accaaacacc acatgttctc acttgtaagc ggaactgaac aatgagaaca cacggacaca 180
gggatgagat caacacacac tggggcctga tgcaggggcc gtagcgggga gagcatcagg 240
ataactagct aatgcatgtg gggcttaata cctaggtgat aggttgatag gtgcagcaaa 300
ccaccatggg acacgtttac ctatgtaaca aaccgcacat cctgcacttg tatccagaac 360
ttwaaatatt ttaaaaayct ttagagawtm caaaaaaaaa ggttnttcaa tgnttcccca 420
ttaaattg 428

<210> 181
<211> 2901
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (10)
<223> n equals a,t,g, or c

<400> 181
agagaaagcn ttccattgaa aggtagatac tttgaggagt aaaaagactt ctttgaatgc 60
tggtaaacac cgcatttatt ttgtgtatgc agtttgattt gcacatgtat aaatggagat 120
gcttttcatt tttgtttgga ctgggtttgt gtcactgctc attacagttt gctttttttgt 180
gtgtttgctg tgcgtttgga gatattagtc agtttcttta gtgatatttg tttccttgat 240
gtgccttttc gtttttcttt ggggtttttg gaatctggat gctgttgaag ggcaatagca 300
gactcctcca gctaagagac aggacatgtt cttgagccac tgtagctgtt gaagctggac 360
accagacgct ccctataacc cccccgccag gccatagcgt gwatgcawgt gcacttccac 420
ccacagagga gggtgtgaag ccttgagaac ctcaagaaag ggctggattc tgccatacct 480
ttgggtctac cttgggactg ctggttgcca acgtgtcaac cagcctgtgt tccctgccac 540
ccacgcactt gctgaggtgt ggctgargca gaatcatgtg aatgggtgca tccaaggagt 600
tcagggccct gcttggagaa gaaatamttt agcatcatga aagggaaaga acgtgcaccc 660
ctttttttgtt tctttagtga atgcaagatt taataaaagt gaataatgag cttccccttt 720
gggagtggag cccagtgcag ctcactgaca gggttgacat cagtatgatg tgttggactg 780
aaactgtatg tctgtaggta ggtgtgtgcc ttttagggca gaccacggtg gccaccccat 840
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tggacataaa tagattcatg ctcatttagg aagctgggag tttcgtgaag ctgagggtga 1140
gttcctgtga ttcttgttcg cttcaacaaa aagtgggaga ccaagttttt atagcaaaag 1200
accaaattag ctgtagagtc ttgaatgcag aaaaaaatta ccctagcttt cttagcactt 1260

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cctgttgatt caaaaataat acctacatga aaacatgatt ccaagttgat tgaatgttgt 1440
aggaattact ggtttagagt agcccagttc tcggcctacc ctgctggttg ggatcttact 1500
gtattcttga atgcactggt ttgaaaatat gccagacttc agcccccaag gaaacaaggc 1560
tgcaagaatt tatgaactcc agctggaaaa ggtaaaggtg acctttggct agccacatac 1620
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gtattccttt gaatgcaata atagaggctt ttctgcgtta agggagaagg aatgaccaat 1800
tgaacttaca cattccccag gcaggtccct ttgccggccc ctacaggctg gggtggcccc 1860
tcctgtcctc agggatcaga ctcccagact ggttagttct gcatgtttcc atcaaattaa 1920
aggttattcc ctggccgcct cctggagaaa accaacccca ccctgccagc tgggggcaat 1980
ggggcaggga ttttggcctc tcagaacagc tcctagaggc tgctcatgac tgaatgtttt 2040
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gattctgttc cgccaaatca gcagtctcgt cctgtggatg cagtgactgg aatttcccat 2280
ctgcaaagca tctctgtagc ccagattttg tggagcctta agacactccc tcaatgccac 2340
cctgacccca cggctggaga accctgtgct tatgtggtgg gcagggccac tgttgatgga 2400
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caggacagcg tgtcaggaac ctcagagcag cttcacatct gccaaagctg agagggagcg 2520
aacttgggaa gcattttgct cattgtccta cccaagtatt aatagcataa tagttgatgc 2580
caaaggagat ggtgacgtcc cttccactgt agttgctgtc acaaccttga cgtctttaag 2640
ctaatggccg tttgcatctg tgtcttcaaa cagatcctgg ttacagccat tttgtgtgat 2700
tcacttcggg ggttaagtaa tgcaggattc tgcaaacaag gtgtcgccgt ccaaatgtac 2760
tgtcctggca tagagagcac tgctttgttt tccactgttg tagagaaaac tagggagaac 2820
tttatttttc aataaacttt tcttgtgtga aaaaaaaaaa aaaaaaactc gagggggtgc 2880
ccgtacccaa ttcgccctat c 2901

<210> 182
<211> 290
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (276)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (286)
<223> n equals a,t,g, or c

<400> 182
taatttaggt gacactatag aaggtacgcc tgcaggtacc ggtccggaat tcccgggtcg 60
acccacgcgt ccgataaaac atgattttgt tttctaccct tcaaggtaaa cattaaaaat 120
aargtggtac ttgtgtwctt gtwcataaaa ccaaaattat akttgggaaa aaaataaatt 180
tatatatgaa aatgtcaaaa tcattttaaa agtattattt tcaaataaaa tggagaagct 240
ggtgaaaarw maaaaaaaaa aaaaaaaaaa aagggngccc cttttngggg 290

<210> 183
<211> 641
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (14)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (43)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (55)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (68)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (80)
<223> n equals a,t,g, or c

<400> 183
gttcaggaaa cccncaaggg gggggagtc caaacgggat gcnaggggaa gcttnccttt 60
tcccagcnaa tttgtgttcn ggtttgaaaa gacccaccac aaagcttty ctattttctg 120
atttaaaagt cgcttttgaa tatgaccatg agaaaccaag aaatgctgct tgtgtggtgc 180
tctgcttcct gaggatttgg ctggaagggg attctccgct ggcacatggg agaaggccat 240
cttctgtgtc ggtgctgtga tctgccttgt tctcacttgc tgaggataag ggcatacacg 300
ctgctcctcg ctttcttgtt gcccgacttc gtactaagca gctcaggagc agtcactcag 360
acccaaatgt cttgactgtg ttgtttttaa tcactgtgac ccttaaagta caggccaagt 420
gttgtcaaac accttggcta aaacagtgga gggtgatggg taaagcagta gagggccctc 480
aacccacaca ctggctgaaa ctgccaccaa ctgccacgat gaacccaact gctgtttatg 540
cccccatttt ccttttttttg tatctacacc cacacgattc ccaatgttgg atatttctac 600
atgaataaag caaggatcag tgcctcttat gtaaaaaaaa a 641

<210> 184
<211> 522
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (514)

<223> n equals a,t,g, or c

<400> 184
caccacgtgg ctgtgaaaat gacaaagcat ggtcgtgagc cactatgccc ggccggattt 60
gcccttatta atggttattt cttgtgaaag tttctttttg cctttgcatt ccttttattc 120
tgtttattcc cccatgcctc acccaaagag ttgcacggtc aattggcccg tgaaggggac 180
gcctactttc aaacaaggca gacaggacac gacaggacgg cggctcatag cacagacttt 240
ggattgcagt ggatgggacc agatcctggc tccacttcts gcyagctgtg tggccctggg 300
caagctgctt aacctctctg ggcctcagtt tctccccctg taaactgggg gatgtgaaca 360
gcgcctgcct ccgagtccta aggattggga gtagtcgtgt aaagtgctca ggtccacagg 420
ccatcaatac taatagttaa aaattattct tagaatcttg cttccctcag ctccctgaaa 480
ggccactaag gcaccccagt tgcagaggcc aatnggtccg gg 522

<210> 185
<211> 735
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (197)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (293)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (386)
<223> n equals a,t,g, or c

<400> 185
agtataacca tttaggtgcc agatttgata atcaccagck gctcatksar gtcctatgtt 60
gcaaagttac tcttacsctt tttttacatt rcttgataaa ggcaatsttt aattayrtat 120
ttyctrttaa ctagctggta gagttcatac ctaaagtcag taaataatgt taagaatttt 180
ttccagctga gcaaatngta tgtatctagt tgtaagaaat caagaagagg atataaaata 240
taatcaggat gtggactcta aaacggaata acctctatgt cctgtaactt ttntcactyg 300
taataataca gcattctcac cctrttaaat ggaaatttar agcaccytta aattccggaa 360
taaaattgct atttggatwg aaaaanccct taggcaacat ttattgaata ttaggaaata 420
acttttatgg gattagaatc catttttat agaaaccaaa tttaaaagta tacatatttt 480
aatataagtg ttgtgataat acagtaacca aaattgaaca cacagtttta wagcttttta 540
tatttagtag cagttgaata tatatggcat gttttacata gattaatttt actatttttc 600
tttrtttaaa maagagracc aaattgaaag ccracagata ctgcaratga ctgggatttt 660
tgtttctgyc ttatcttttt gtgttttttt tctgaataaa atattcagag gaaatgcttt 720
tacagaaaaa aaaaa 735

<210> 186
<211> 785
<212> DNA

<213> Homo sapiens

<400> 186
aattcggcac gagagcaagc ggaaccaggt atcgtacgtg cggccagccg agccggcgtt 60
tctggcccgc ttcaaggaac gggtcggcta cagggaggga cccaccgtag agactaagag 120
aattcagcct cagcccccag atgaagatgg ggatcacagt gacaaagaag atgaacagcc 180
tcaagtggtg gttttaaaaa agggagacct gtcagttgaa gaagtcatga aaattaaagc 240
agaaataaag gctgccaaag cagatgaaga accaactcca gccgatggaa gaatcatata 300
tcgaaaacca gtcaagcatc cctcagatga aaaatattca ggtttaacag caagctcaaa 360
aaagaagaag ccaaatgaag atgaagtaaa tcaggactcg gtcaaaaaga actcacaaaa 420
acaaattaaa aatagtagcc tcctttcttt tgacaacgaa gatgaaaatg agtaagtgta 480
aatattttga atttagtcta ctttgaaagt atatggagtg ttcattaaaa tcacattttt 540
tcctattata aagatactac aagttcttta tagaaagttt aggaaataga gaaaaaaatt 600
taataaacta catctattca tcaatacccc tctgacttaa aatgccaact ctatagaaat 660
tagctagtat taacattttg ttatttccct tgtgtggttg tatatatatg taaattatat 720
ttttaagcaa aatacatttt ttgtgtgtaa acaaaatttt ataaatacaa ctgtattgca 780
aaaaa 785

<210> 187
<211> 1679
<212> DNA
<213> Homo sapiens

<400> 187
gatctttagg tttttcctat agaaaacatt cttcctccat cagtagccct ttatttgata 60
ttcagaagtg gaaagctttt tcattctcca gtagaacttt taaaaattgt tacagatacc 120
tagctcttca cagatatcat gtattgtaaa cagtcatgtg tcttaatttt attttctcta 180
tttgagtgca taattatcct aataatccca aagacactga caactcaagg aacagcagta 240
cagtactatt agaagttaag tatgttgttg ttatttcaca tttcatttaa ttgtggataa 300
atgttagaca tctgttgaaa taagctcata tggtggaaac gacaactata ttatgaatta 360
ttttcagaaa tggatctttg aatagcagat caggatttaa ataataaaat tatctatgaa 420
tcacttttat ggtcatacat atatgataca aatccagagt tattggtgca gaaatggcta 480
cccgagagct tggtaaattt gccttggttt cttatgttaa atgtattgtg cttcccttct 540
gtctctagaa tgtggctctt cagaagacag acaatcgaca tttaaatttt tccaaacaat 600
gaaaaactaa attaaaaaca ttgcttgata tttcatttaa aattgcacct tgcttaaggt 660
ttactgaata actgaaatgt cagcaattta aaataaattc aattgtgtga taaaatatct 720
cacctataat agaagaaaag gaaaatcata ttatttggca attttgcagc attgtggttg 780
cctaacaggt atatccagca gatgagaaac agtatgaaag gattgtatta acatggtaag 840
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aatacgtttt cttgktttat catctgktct atgattcggc ttcactttgt gtggktattg 960
aattatgtaa cagagatttg gktttcccaa aatgktatca catttgaaac tatgattgct 1020
ttgkgktcag tccttttgga acacgtagct tycagcttaa gggtagagga aatatatacc 1080
taaaatcatc aatacatgaa agaaaaagga tggaaactat gtcctcagtt ttacttctac 1140
caaaacatcc ctgtatgtgt gtgcatgtat gttggcgtgt gtgtgtgtgc atgcatatta 1200
gtaaatgtgt gtttgcatgt gtgtgttggg gagtgtatgt gatctgggtg tttgtttatc 1260
tctgttatta ttccccttta gctttatttt agtcaactct acattatgat gaatttcaaa 1320
atgaagctgt attaaaataa ttgtaatata acaattcaat ctcacatgtt actgcagata 1380
gttaactttt gctgcaatct attgtacatt tgcaattttc tgtgttagta aacttagcag 1440
aatctggtta wttattttwg tgtaggctta atgttcactg aaagataagt caattactgy 1500
tagtaaaaaa ttaaggtact ctcactgcag agatttaagc ctgggcctaa tgtgctgtat 1560
tatgaagcct tgtgactgaa aaatatgttt acatatgttg tctatttttt taataaactt 1620

ttatagctgg tctatttgct cagtaaaaaa aaaaaaaaaa aaaaaaaaaa aaactcgag 1679

<210> 188
<211> 780
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (289)
<223> n equals a,t,g, or c

<400> 188
cggtgggctc gcgttgaggc tgcggtcatg gagggagcag gagctggatc cggcttccgg 60
aaggagctgg tgagcaggct gctgcacctg cacttcaagg atgacaagac caaagtgagc 120
ggggacgcgc tgcagctcat ggtggagttg ctgaaggtct tcgttgtgga agcagcagtc 180
cgcggcgtgc ggcaggccca ggcagaagac gcgctccgtg tggacgtgga ccagctggag 240
aaggtgcttc gcagctgctc tggacttcta gggatctcag ccgtggckna ggccaccccc 300
agaggagccc ctggtccaca gaagcaggcc ttgtgtttcc agcggcctct gataagaggc 360
agggaaggam ctgaaggatt tggarttgat tcaaacaaga tctctgggag tctccagcct 420
gtgcagaagg ggcaggactg cagtgcactg cgggccttgg agtgtccagt ggggacactg 480
gtgtgggaag gggcagcacc tggggagtcc ctgcctctcc tccctgggac aatagtgtgc 540
atgccacccg gggtcctaca ggcaggtgct gggaaaggcc tggccagcag gtagcctgtg 600
tgtttgacaa acagcagctg gcagcgctgc ctcctgccca cattcctgcc acccgacatc 660
aaagctggcg tgtgaccttt ccagccatgc gatattcccc ttggaagatg cttccccagg 720
ctataaattt gttctcacaa agcaacatca ataaatcaaa actgtctcty ccaaaaaaaa 780

<210> 189
<211> 533
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (485)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (498)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (522)
<223> n equals a,t,g, or c

<400> 189
ggtcccttta aggtttgctt ctacagcccg tggactttag cctaaacacg gacccgcgaa 60
gctggcttta tttgtccatg tctcggacag agcctgggaa gctgccagtg agatttcaga 120
gaccaagagc gcgaaggggc gggcgatgtg gcaatccgtc tgggatgtga aaagcgtgga 180

gcgcatttag aggcattcga cgaaaacaca ggaaatcact cctctcccgc tcctgggcgc 240
cgctgccact ggggcagagg actgggaacc gcggcagcgg gataagtggc ccagccagag 300
agcgcagctc ccgcgcccgg tcctgccctg cgaaccacgc ggccccctgg gctgaagctg 360
ctccggccat ggccctcggc cccgcgcccg cccargggty gctgtcccct gcttgctggg 420
ctcctccctg gtacattgcc tcctcccgga cacaaattac tccctgaaaa aaaggcccctt 480
tgttnaacct actgtggnta accgcctttc aaaaactaaa anttgctggg gaa 533

<210> 190
<211> 602
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (548)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (583)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (590)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (600)
<223> n equals a,t,g, or c

<400> 190
tccttaatct tggttttcct taaactttct ataagtccag catctgaaat attttgtcaa 60
ttatcacatt aatgtgttca ttttgtaagt aagagtactc aatttaaaat gatcttactt 120
taaaagtggc ctagtttgca gtgcccagca ggacactgac agtcacagct gtgtgacttt 180
ttgtgggtta cttaattttt ttgagcctcc ttttctcttc tattcaatga ggataatagg 240
gcctacctca taggattatw atgcattccc ctctgttaat gcacgtaaag tttttacttg 300
gaaaactaac tcaccattta acaaccattc taagcaccat agaatatatt ttgtttcaca 360
aatttggtat tcattcagaa taagtatttg aaaagtgagt aaattctatg caattatagt 420
tattaaatga cttataaact gtgtttctct tccacttctt gctacattta atcttctagg 480
tgttcagata tctttggaga ttataggcag caataaagct aaggcagcta acctttaaca 540
ttcttggngt caagctaata ttttggtgaa agggaattct tgnggttctn aaaaaacttn 600
ga 602

<210> 191
<211> 858
<212> DNA
<213> Homo sapiens

<220>

<221> misc feature
<222> (772)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (801)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (814)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (815)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (852)
<223> n equals a,t,g, or c

<400> 191
cttggctcaa acaatatttt ccctataaca aaggcaatag gacacaaaat tcacatcctg 60
ctgggccttt tttcatcaag tcagggtgat ataaaaacat tggaagtctt ttcaccaaac 120
cctgacttta ttgaatgcta gtagaagatg tagaattaga gacatctgat ttgtttatca 180
ccttagcaga aaaaccacag tccaaaagac aagcaaatta agaatggagc ttaaccatgc 240
ctccattggg aagtctagac tttgagccag gtacagtaag aaaaattagc ctctgattca 300
ttaagtttgc cacatgactt attttgatat tttggataca ttaactcact taggagaatt 360
cagaaaagaa tgggtgatta aagttcatta cagctgaata aatgtgtcta aaacagactc 420
ttgtattctg aaagtacagt ctacaactga taaaacctta tgattctttt ctccccccatt 480
atgcccctat atatatcaag atttgggtac tttattttag tagaaaatat atatctttta 540
catatgtatg tatttataaa tgcatagata tatgtataaa aatttgtaag cgttagcggc 600
attaattcac caatgcattt ggacaacttg atgtaactga ctttatttta tgtgactata 660
ataaaaagca taattttctc aaaaaaaaaa aaaaaaaaaa aaaaaagggc ggccgctcta 720
gaggatccaa gcttacgtac gcgtgcatgc gacgtcatag ctcttctata gngtcaccta 780
aattcaattc actggcccgt ngttttacaa cgtnntgact gggaaaaccc tggcgttacc 840
caacttaatc gncttgca 858

<210> 192
<211> 667
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (82)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (234)
<223> n equals a,t,g, or c

<400> 192
gcgggggaag cggggctgta gctgggcagg gagagggcgg acgaaatcgg tagcgatctc 60
ggctgcggcg ctgcccactt gncccggccc gcggggcgcg ccctgaccct tcatctttgg 120
gcaggctcga gggcgcgcgc acggttggcg ttctggggcc tcaaactcct gggccttgac 180
cgggcaggcc gcgtctcccc gggtgtgagt ccaccgggac ccggccgccg cctnaagcgc 240
gkgcgccaca gaagcggcgg cgcccgaaga cgcgctcctg gctcggcccg acagcctcgc 300
ttggccgcca gttcttctgc agccgaaggc ggttgttctt ttaaagaatt attgaagacg 360
aaggtttttt tctttttatt tttttaatgg ytttacagaa tcttaaatag aatacagttt 420
gacatgacgg caaaaaatgt tggtttgact tccacaaatg cagaagtaag aggatttata 480
gatcagaatc tcagtccaac aaaaggcaac atttcatttg ttgcatttcc agtttccaat 540
accaactcac ctacaaagat tttaccaaaa accttaggac caataaatgt gaatgttgga 600
ccccaaatgt gatagaaaac gggctagaaa atttatagac tctgattttt cagaaagtaa 660
acgaagc 667

<210> 193
<211> 537
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (85)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (511)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (537)
<223> n equals a,t,g, or c

<400> 193
gttaccgctc tataccggca gcagccgcgg agagcatgcc ccgcccccgt ggagcccacc 60
ccgggcggtt aacctcgggt ctcantcccg ggctgtgacc ctcccсgagg ccccgccccc 120
acggcgaagg cccggggcag ttaacccttc tcttgctgcg gcagagtccg cacccgggca 180
ggcccatctc agaattaacg ctttgatggc atcaccgcgt cgggaatccc tggggatggt 240
gttctccacc gtcaagacct ttgagccgcc tgagcgacta actcctgcgc ccctgagggg 300
acattttatt cagaaattaa atcattcaga gttccagcac tgtcgggggt catcgggctc 360
tgtccaccgc catagcctag cattgtcacc aacggagcca trgagggacc tcggcccaag 420
ctggggcctc ttcattgtcg aaaaggcctc ttgccagacc aggatctgtg ggcgcggcca 480
ggctggagga ctagggcggt ggcagtggca ngtgagtgca catggctgtg ggtggtn 537

<210> 194

<211> 400
<212> DNA
<213> Homo sapiens

<400> 194
tctaactata ttaaaaaatt tctgtatggg gatatcatta ggaagggtat cagtaccttg 60
tctgtwatgt gtctactaag caaaacccaa actgcagcac ccccctgtgg tacactgcac 120
ctccagtttg tactgggggt tgttggccag gctataggca tctttcacag gtccttgctt 180
agcatcccaa gtactgtgaa tacatgttga ttctttaaaa agacctggat tccaactcaa 240
ataaatcaca tcataatact ggcagagatc atcccaggaa atccaaaata ttccgttgtc 300
tattttctga gctgttcggg gatcaaagtt taaatacttt tgcaactctg gagtccagtt 360
ttttacatca ttttcactgt atcttccttt ccaacgtaac 400

<210> 195
<211> 431
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (411)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (417)
<223> n equals a,t,g, or c

<400> 195
cgcgtgggcg gacgcgtggg gtgaattttc agccctcaga gcagaaaatg agaaaataaa 60
actcgaacta catcagttaa aacaacaagt aatggatgaa gtgatcaaag tccgaacaga 120
taccaaatta gacttcaacc tagaaaagag cagagtaaaa gaattgtatt cattgaacga 180
aaagaagctg ctggaattga gaacagaaat agtggcattg catgcccagc aagatcgggc 240
ccttacccag acagacagga agatcgaaac tgaggttgct ggcctcaaaa ccatgcttga 300
gtcacacaag cttgataata ttaaatattt agcagggtct atwtttacst gcytaacagt 360
agctctggga ttttatcgcc tgtggatcta ataaagtgtc tatttaaagg ngaaaanaaa 420
aaaaaaaaag g 431

<210> 196
<211> 417
<212> DNA
<213> Homo sapiens

<400> 196
tttcactttc tacttttttc attttgttct gttcgaattt tttataagta tgtattactt 60
ttgtaatcag aatttttaga aagtattttg ctgatttaaa ggcttaggca tgttcaaacg 120
cctgcaaaac tacttatcac tcagctttag tttttctaat ccaagaaggc agggcagtta 180
acctttttgg tgccaatgtg aaatgtaaat gattttatgt ttttcctgct ttgtggatga 240
araatatttc tgagtggtag ttttttgaca ggtagaccat gtcttatctt gtttcaaaat 300
aagtatttct gattttgtaa aatgaaatat aaaatatgtc tcagatcttc caattaatta 360
gtaaggattc atccttaatc cttgctagtt taagcctgcc taagtcactt actaaaa 417

<210> 197
<211> 734
<212> DNA
<213> Homo sapiens

<400> 197
agacatattg aggtgcctgc ccttgtggag tattcatttt atgctgccca agatatcatt 60
taatttagac ttaacaagta tttccttgtg attatattac tctgtccttg ttaataaagt 120
gctgctgtgt ttgactctga acatactacc aaaacttctt caaagagttt tttatgaaag 180
actttcctcc tttacaagar agaaatrggg tgctgccttt ctgtttagta aaagcagaat 240
ttgcagtggc atctaaagag acttttttaa ataaaaatta tgtattgtgg cataatcctt 300
tttttgagct ctacagagaa cagtcttttg gtaatagtgg caggtattta ttccttctga 360
atatataccc cattatagga ataactgtta cttatttagg attccatcat tgaaaatttt 420
gacccaaggc acagcagtga aatttatagt tcycaattta gttgtcatta ttgacaggca 480
ttggtattat tagtcattgc taagcaacta aaacttcatc agttcaaata agttttaatt 540
gtcaaatgaa gtataaacac atgaactttc tagaaatatt tcctcttttg gataggtctt 600
taaccagttc atatatatac tttgtcaaat atatggatgt gtatgtgtac atttataaga 660
accagtatgg atacatccat tcactgtggt acattttaaa ataaaatatt ttagcagtga 720
atatggaaaa aaaa 734

<210> 198
<211> 606
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (144)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (155)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (598)
<223> n equals a,t,g, or c

<400> 198
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ctatttycag cttttcctca attnacattt tggtngtata cttcagagtg atgttatcta 180
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ctggggagat gtgctttttt ggaaaactca aaggtgctag ctccctgatt caaagaaata 300
tttctcatgt ttgttcattc tagtttatat tttcatttaa aatcctttag gttaagttta 360
agctttttaa aagttagtta aaagaattga gacacaatac taatactgta ggaattggtg 420
aggccttgac ttaaaacttt ctttgtactg tgatttcctt ttgggtgtat tttgctaagt 480
gaaacttgtt aaattttttg ttaactaaat ttttttctta aaataaagac tttttcacaa 540

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wraaaaaaaa aaaaaaaaaa actcgagggg gggcccgtac ccaatcgcct gtgatgtntc 600
gtatac                                                            606

<210> 199
<211> 373
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (251)
<223> n equals a,t,g, or c

<400> 199
catcttggag gtcaaataat agtaggaaaa gttcagcaga tactgaattt tctgatgagt 60
gtactactgc agaaagagta ctgatgaaat ctccatctcc agcattacac ccacctcaga 120
agtacaaaga tagaggaatt ttacatccta aacgaggtac tgaggaccga tcagatcagt 180
cttctctgaa atctacagac agcagtagtt acccaagtcc ttgtgctagt ccttctcctc 240
catcctcagg naaagggctc aaaatctcct tcrccaagac caaacatgcc tgttcgatac 300
ttcataatga agagtagcaa tttgagaaac cttgaaattt ctcaacagaa gggtatctgg 360
gctacaacty cta                                                    373

<210> 200
<211> 3652
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (306)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1412)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1519)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2101)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2102)
<223> n equals a,t,g, or c
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<400> 200
acgagctgat gtctcccgga ggaatctgca attgcataat ttagttggtt gcttgtctac 60
tgtctctctc tttggcaaga atgaaagctc tatgagcaaa cagaccttgt ctgccttatg 120
atccatttta ttactagagc ctaggactgt taaattcatt aataaagtct ttccatcact 180
ttttgttctt tatattcctt tactcaattg atattcagca tgtgcagaac agttcttttc 240
caaggctgca taaaagtttt ggaatgaggc acataaataa tatccttcta ccaataaatg 300
ctatcngtta taaaatagtt tttattttat aatcactgaa tatgtcaaaa ctttacagtt 360
caggcctttt gaatcaaatg caaaatcaaa tatgaaaagg ttaatgatct tgtccactaa 420
aattgtagtt tgccatacag gaaaatagac tcttaaaaat gataaaaaaa aaaaaatcat 480
tcttaaggaa acatattaat aagacattta aaaggctaa gatctttaat gtgaaaaata 540
ataagataaa gatgacaacc actgaagaga agaaaaaacg ttttatgttt tttctaaatg 600
tgtgtaaaaa caaaatcttg tacctaccaa aatgacactt ttttcaaaga aaggtatcaa 660
atgtgtatac tttaacacac agcccttcct tgtgtaaata tataggaaat ccttaaagga 720
gcataaaaca atttacttag aaattctata cttaaactta ttcaaaggaa ataattaaag 780
gtgtgtaaat aagatatgca tagcattgct ctaaatgtca aatagtaggg aactaggtaa 840
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gtagccatca aaaggatacc atagaacaga acttattgat gtgaaaagat gattaaaatg 960
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<210> 201
<211> 551
<212> DNA
<213> Homo sapiens

<400> 201
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caagcacctg gagtcctttt acgaaaaacc tcctcctggg cttatcaagg aagatgagac 120
taagccagaa gattgcatac cagatgtacc aggcaatgaa cacgccaggg aatttytggc 180
tcatgcacca actaaaggac tttggatgcc actggggaaa gaagtcaaag ttatgcagtg 240
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ggcaaccaaa agttagagca gttcagagtg gcacatgaag atcccatgta tgacatcata 360
cgagacaata aacgacatga aaaggacgta aggatacagc agttaaaaca gttactggag 420
gattctacct cagatgaaga taggagcagc tccagttcct ctgaaggtaa agagaamcac 480
aagcaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540
aaaagggggg g 551

<210> 202
<211> 665
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (463)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (471)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (582)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (612)
<223> n equals a,t,g, or c

<400> 202
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aagaacagtt tgggtcactt gacatggttc tccaaaggga tkttatgggt tgtwtttggt 360
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tgtcaaatct caagtgtagc ttatatttta tgttcctaga gangttgtca nggaaagatt 480
tgaccctttg gcaaatctgt ttgaatagag atactaccat gctgcccaat aaggctttct 540
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gatccatgtt tnttaccatg ccaaattaat tgaaggaatt ttcctaaaag gtatctcccc 660
tcggt 665

<210> 203
<211> 2102
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1861)
<223> n equals a,t,g, or c

<400> 203
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gctctacaaa taccaagtat ttattgtggt atatttttag aatgtagcca tacagtgtaa 120
ttatgggtat ctgtcatgga tcacaattat tattcatagt aagtcattgt gatacagaag 180
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tgtccttcag ggatataaaa agaaaaacaa atctgttttt tgagctaaaa gagcacatcc 300
aaacaagaat ttaactggct aaaatttagt aattactgtt aagtaactat caaacttgaa 360
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tctgcttggg tctccgctgc cccagccaca cacatcctag aattcttgta aacatatctg 540
gctctgtgtt aacagtgcac ttgttatatg ttttctaaga gattagttct tcctgtgatt 600
tttccaagta cgctgaaagt agtagtatga acttaaggag gctagtcaaa gaaacttgga 660
gttataggta tttttaaaga ataaatcctc aattccatca tcacttggcg gggagggggc 720
acttattaag cattttagat aataaaactg gttaagctta ctctggtaga acagacaatc 780
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aaaaaagttt tacttttatt ataaaacttc atctatggtc aaagtaaaca ctgttacatt 1440
taaattgctt tttaaaaaca attgcgatct aaaaagtcaa aaatctgaaa tttaataata 1500
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nctaactatt aagagatttc ttcctttctt gagtaacaaa tttggtgatt atattctttc 1920
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aaatgaccct tcacctctta agggaaaaca gcctccgcca ttccctttca aaactatact 2040
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tt 2102

<210> 204
<211> 283
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (181)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (282)
<223> n equals a,t,g, or c

<400> 204
aactgatatt taataatatt taatattgct ctaaaatttc tggctaaaat gaaaatattc 60
aaccatcagg aaggagaaac aaaactatta ctgtttgtaa acagtttatc atcagtactt 120
acctaaaaat cctggagaat gagctcagaa atatttctaa gagttgagac agtttagcaa 180
natgaacaga tacaacctca aaccaaacca aactagaaag ctcagaggac acagaatgcc 240
agtactgggc tgggcaacac ctctgttgtt tgtgaaaatg tnc 283

<210> 205
<211> 425
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (34)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (77)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (424)
<223> n equals a,t,g, or c

<400> 205
ccacaccccc ataaggccat ccaaatattt aaangccccc ccagtgggaa atttggtgtt 60
taaaacctca atggaancct aatatttccc ttatgtccgt tagtcccctg taaaatgtta 120
ggtcacccca aggaaagggg agaaatagca atggttgttc ctaaggtatt gcttgccctc 180
catgtcttcc taaagagcag aacttggagt ttctccttta tgtagagaag aagtwactta 240
gggtgtattt gcaatgaaat attcatagat attgaaagct tgtgtttaca tkaaatatgt 300
ttattatcaa gaagtccttt ttccaattct gtacattaaa tatatgtgtt ttaaaaaaaa 360
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aagggggggg 420
gggnc 425

<210> 206
<211> 483
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (444)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (469)
<223> n equals a,t,g, or c

<400> 206
cccacgcgtg grcagaccgc gcagggagca cacaccgcca gtctgtgcgc tgagtcggag 60
ccagaggccg cggggacacc gggccatgca cgccccccaac tgaagctgca tctcaaagcc 120
gaagattcca gcagcccagg ggatttcaaa gagctcagac tcagaggaac atctgcggag 180
agaccccсga agccctctcc agggcagtcc tcatccagac gctccgctag tgcagacagg 240
agcgcgcagt ggccccggct cgccgcgcya tggagcggat ccccagcgcg caaccacccc 300
ccgcctgcct gcccaaagca ccgggactgg agcacggaga cctaccaggg atgtaccctg 360
cccacatgta ccaagtgtac aagtcaagac ggggaataaa gcggasgrrg gacagcaagg 420
agacctacaa attgccgsam cggntcatcg agaaaagaga cktgacggnt taamgaktga 480
tcg 483

<210> 207
<211> 976
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (193)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (929)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (958)
<223> n equals a,t,g, or c

<400> 207
agctttcagc aagagatggt cacaatcaga aggataatac aaagtcaaaa gagaaggaga 60
gtgaaaacgc ttccaggaga tggtaaagga aataagcata agaaacacag aaaaagaaga 120
aaaggggagg aaagtgaggg ttttctgaac ccagagttat tagagacttc taggaaatca 180
agagaaccta cangtgttga agaaaataaa acagactcat tgtttgttct cccaagtaga 240
gatgatgcca cacctgttag agatgaacca atggatgcag aatcawtcac ttttaaatcm 300
gtgtctgaaa aagacmagag agaaagggat aaaccaaaag caaagggtga taaaaccaaa 360
cggaagaatg atggatctgc tgtgtccaaa aaagaaaata ttgtaaaacc tgctaaagga 420
ccccaagaaa aagtagatgg agaacgtgag agatctccct cgatctgaac ctcccaatta 480
aaaaagccca aagaggagac tccgaagact gacaatacta aatcatcatc ttcctctcag 540
aaggatgaaa aaatcactgg aacccccaga aaagctcact ctaaatcagc aaaagaacac 600
caagaaacaa aaccagtcaa agaggaaaaa gtgaagaagg actattccaa agatgtcaaa 660
tcagaaaagc taacaactaa ggaagaaaag gccaagaagc ctaatgagaa aaacaaacca 720
cttgataata agggagaaaa aagaaaaaga aaaactgaag aaaaaggcgt agataaagat 780
tttgagtctt cttcaatgaa aatctcgaaa ctagaagtga ctgaaatagt gaaaccatgc 840
accaaagcgc aaaatggaac ctgatactga aaaaatggwt aggacccctg aaaaggacaa 900
atttctttaa gtgcgccacc aaaaaaatnc aaactcaaca grgaaactgg gaagaaantt 960
gggagttmcc gaaatt 976

<210> 208
<211> 660
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (560)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (567)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (583)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (589)
<223> n equals a,t,g, or c

<400> 208
ccacgcgtcc gccgacacgt cgggattggc ggctgcagcc aggggtcctc cgacgctggg 60
cttccgtgag cggcgctctg ccaggtgggg ccggagctgc ggggagggag ttggcgccta 120
gcgcgcactc catccccgcc tctgcagtgg actcggccgc agaatcgggg tcccgggctc 180
ctggaacttg tcccscccag gccgcggcga ggaggtcact ccagccgatc tctggaccgg 240
attcgtccca ttctcgtcct catggtggac aagaaactgg tggtggtttt cggaggcaca 300
ggtgcccagg gtggctccgt ggcccgcaca ctcctggaag atgggacatt caaggttcga 360
gtggtgaccc gaaaccctag gaagaaggca gcaaaggagc tgaggctgca aggtgcagaa 420
gtagtgcagg gagaccaaga tgaccaggtc atcatggagc tggccctgaa tggggcttac 480
gscaccttya tcgtgaccaa ttatgggaga gctkcagcca ggagcaggag gtmaagcagg 540
ggaagcttct tgctgatctn gccaagngcc ttgggcttca ctntgtggnc ttcaaggggc 600
cttgaggaca ataaagaagg ttacgggaag ggagatttgc cgccggggaa cttttaccgg 660

<210> 209
<211> 514
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (56)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (464)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (467)
<223> n equals a,t,g, or c

<400> 209
tggaaccaat ctttgtggta catattccag ctttttgaat gagtgcatat ccagtnagta 60
cctttaaagt aacactttgt acataacaar tactcagcaa atgtgaaact ttatttgctc 120
ttacttcaaa attagtccaa aatgttggaa ataaaatata agacattgat ctagatatga 180
ggtttttctc cttcattctc agctgtcgaa gaaatcraag tagcatatgc acaaggwtaa 240
aaaccacata tacaaatact atagaacagc ttataatgaa aaccttgcct gcctttataa 300
aaaatgtgat tatcttcttc tgttaatgtc aataaaagat ggtttgtcct agaaggtcta 360
taaatggtat tatgttctgg agggtttaca tatgaaaaat gtagaaaata caaaaagtgt 420
ctatatatac aaaaatgtaa gtgttaacat ttttatattt gccntcnagc ttttttttta 480
aataaaagga atgccatatt gccattaaaa aaaa 514

<210> 210
<211> 173
<212> DNA

<213> Homo sapiens

<400> 210
gtcaatgctc tgaaatctgt ggagcaaacc acagtttcat gcccatcgtc ctagaattaa 60
ttcccctaaa aatctttgaa atagggcccg tatttaccct atagcacccc ctctaccccc 120
tctagagcca aaaaaaaaaa aaaaaaaaaa aaaaccctgg ggggggggcc cgg 173

<210> 211
<211> 1521
<212> DNA
<213> Homo sapiens

<400> 211
gctatcaaaa tcatgacatt atgtcacttg gagcaacaca gttgacccgc caaggcagcc 60
tcttcctcca tagatggatg aacgctgtgg ccgctgctcc tkcmctggcc atgccctgay 120
gctgccaaca ccactgctcc tctatttata agtcttarta gagttgctga cccagcaata 180
actgaacagc tgatatgtac ctcacactaa gccaggcgct tcatatgtat ctaacttgaa 240
aaatgctgag ctagttacct taacaccatt aacttttact taaaagtttg tttttctttt 300
ttaatcccag tgagctccaa acaagtttta ggaggctccc caaaaccagt gaagacttta 360
actaaaagta gaatttcaaa gtattagaaa ccaaacccca aaattaaatg tgaagatcag 420
tgtctgtact gagctggccc atctggtgga cacaggattt gcgttatcga ctgcaatgtt 480
acccaggatt cacgatttct agcatctgtc agggttaaga aaattggatt gagtaccaaa 540
tacagcagag caaacccggc tttgaggcaa gggccccatc aagtagtcat gcagtacttt 600
tgttagggtt ctgggtgcaa atcttcctcg tccctcccac cttctcctgg cctccttgta 660
aacccaaacc gccaggtacc tcaattttct tcaagaccag gctgttctta atgttggtaa 720
attggtcaag gaaatgggtg agccactgct tgctctgcac atcgtcctca gagtgctcgg 780
tcttcaggca gtacagcagc tgcatggctt tggcctgcag gagtaagtgg cccattccta 840
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tgctcctctt ggaggcagag aagcagtagg agtcggtggt gaaatggccc tgtgtgaatg 1320
tggaagacca gcagattgga ggtggaattg gcctcagtgc ttgtcctgga ggtggagaag 1380
cggtcagagt ccttggtggt gaagtggccc tgcacaaaac gttgctcccc cttggccggt 1440
gaaagaataa aagaaagctg gccacttgca aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1500
aaaaaaaaaa aaaaaactcg a 1521

<210> 212
<211> 1875
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1052)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (1291)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1849)
<223> n equals a,t,g, or c

<400> 212
gtctgctgtt gtcagaaggc agggagggtg atgaaggact gacccacatg gactgggatg 60
tgtgtcggtt atgggcatga ctgcacgttc actctcagtg ggatctgggc aacatggagt 120
tcattgtcct gttgcttact tactgcaatg tctttggccc tccttttcaa ctggttcctc 180
tgttgggccc aaaggttggg agtaggagac agtatcccag gctgacaagg gcttgccytt 240
taccttgggc accttgttaa tttttagcct gtgcccttcc ccacctttgc cctcccagtg 300
gttggtatgt gggaagccca tctcagttcc tgtgacttca tgtctcaaac caaggatgag 360
cgtctggtct ctgctatgat ggtggtatcc gaggcctttc cctgcccagt ctggtgcctg 420
ccccacattg taccggacac tggattcctg gaccccсttc tcctttcctt tctttccttc 480
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ggtttggggc acaaggaagc cttagggtat ggggaaaggc tgttattacc tagagtttac 600
tcccaggcca gggggctgcc atcttcttca cagacatccc tgaaaggaag cccctttggg 660
gcagggaggt gaggacttca tctcaacatc ggctggtggt tggtagggga gcttttyctt 720
ttctttcctt tttttttgtt tttgtttttg tttttgtttt tggtaacatg ttaggagtta 780
atgttgcaaa gagtagttta catcttcact ttctgaagac acttgaattt aggaccgatg 840
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gtaattatgc ttttcttttt aatacaaaaa aatgtataaa aataaacact tgaaaaggca 1800
aaaaaaaaaa aaaaaaaaaa aaaactcgag ggggggcccg tacccaatnc gccggatagt 1860
gatcgtataa caatc 1875

<210> 213
<211> 1917
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (798)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (802)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1073)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1748)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1829)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1887)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1891)
<223> n equals a,t,g, or c

<400> 213
gaattcggca cgaggcagtg gtgtgatctc agctcactgc aacctccacg tcttgggttc 60
atgcaattgt cctgcctcag cctcccaagt agctgggatt acagacatgt gccaccatgc 120
ccggctaatt tttgtatttt tagtagagac ggggtttcac tatgttggtc aggctgatct 180
caaactcctg acctcaagtg atccaccccc ctcggcctcc caaagtgcta ggattacagg 240
catgagccac catgtctggc cctacttttc ttttatgcct tctttttgga ttaatcaaat 300
atttagtttc attaccccac tattaacttt ttctattata tattcttttt ttaattaagt 360
gattaccctt gggttgttac atacatcctg aacttcttat agtaaatata catgattaat 420
ttaacctctt ccctagcaat gctcagattt tagaacatta taattccatt tagtctcttc 480
taccttttgt tttattgttt tcatgtattg taatcctaaa catattttac accccacaag 540
acaatatatt agtgttgcat atcctcaata ttcatttaga ttaatccata caattactct 600
ttctattgtc tttcactcct tactgaattt ctaggctttt atctgaaatt attttccttc 660
tgcctgaaga actacctttt atagtaattt tagtgtaatt ctgcttarga agtattatct 720
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ggtgtatttt ctgggtcngt antyctagat tacagttact ttcttcacta cttatattct 840
cactgccacc attttattga aagtcagcac caaatcaatt aaaaactgaa ggtaatattt 900
ctccccctca ggctgttawa aattttttc yttgaccttg gtttttawta gkgttactgt 960
aatgtgccaa gatgtgmctt tctttawatt catcctgctt gggattttca ggaattcatg 1020
cctcagggct ttatgtcttt cattagtttt gggaaaattt taagccatta acntttcaaa 1080

gatcatctct tccctattct ctcttyctct ctctgctatc cttttgraac tccaattmca 1140
tgaaagttag atttgttcat gttattcctt acgtttctta tgttcttttt tatattttcc 1200
atctttttcc ctctctgagt gtcagctctg tgataaggta gtcttgagga cttgtgtctg 1260
ctggaaggaa ctgatctgac ttggagamcc tcaaaaaagc tctatctctg gatattcatg 1320
aaaagaatag caattagaag caatctgctc aaagtcagca ttgcaactgc ttagggctgc 1380
aatataggtt gaggcaccaa gagactagca aatattttat agggttacct gagaaacaag 1440
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aaggttgtgt gcatgttcaa ggctgcatgc atgttcagga aataccaaca ggggccaagt 1560
tacttattca tctcttactg accttggagc tcagtgtaag caggcaatga aacctaaggc 1620
aaatttataa actgcctgaa ctttgaaggc atgtggaaac tcataaacag cttctctcag 1680
ccagttgcag aagatttact tattcaagtc atttaagaaa accttctaac ccaaaatttc 1740
ccatgctncc tgagatgacc aggacctaga agtagctaaa atagaacaga tttaaaaagt 1800
acataattct gtggagatct gaggctttna ctagcttgaa tgtacaacac acaacctgtg 1860
ggtgggataa attaagcata aacttgngta naaaaaaaaa actcaggggc cggccat 1917

<210> 214
<211> 1544
<212> DNA
<213> Homo sapiens

<400> 214
ggcacgagct atagcaatct gggttttctt agccaattga aatgggcatt tattagatca 60
tttaagcatc atatcaatat agtatatttg gcgactttat gataagttct tatgatagat 120
gttcaaaact ctgctcaggt gacattttta tggatccaca tagtttttgt catatatgaa 180
aagaaagcat tgagttgtgc agatggttaa atgtgcattg agttatttct ctggaatttg 240
catgagaatg gaccgacttg tagttgtatt aacttttcta gtgcccaggt tagaaagttt 300
gatctgtgta gtttttaaag gcagcatcca aatcacttat attcagaaga aaatggtaac 360
agatttagaa gctgtctata ttttccccat tatccataat acatattatt ggcaatatgg 420
ttttcactct ttgttgttaa cgtatcaaca atgtgcaata gccactaata atcatttgtt 480
aatgcatgct tccaagttct gtatttgaaa atctcagact tcatatatgg taagtgatgg 540
agtaatttat aacttttatg ttgaattctt gctactttaa aaaattgtgc ttctcctttt 600
ttaaagcata tgacttactt aacagctgat agtcagttac ctggattttt agtatttttt 660
tacatcacaa aaagatttct ctgaagtttg cgcaggggtc tatttgtagg cagtttccaa 720
cttactaata agtaaggttc tgaaagttat aagttagctg tctggaatag atagtctcat 780
agaaaccagg ttgtagatgg tgatttggtt ccttgggcaa cctactgaaa cccatttact 840
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gaaatcaaaa aacctattga gatggaattt gggaggaaag gaggacttac tgatatccct 1080
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cactttggga ggccgaggcg ggcagatcac ggggtcagga gatcgagacc atcctggcta 1320
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gcctgtaatc ccagctactc aggaggcgga ggcaggagaa tggcgcgaac ccgggaggcg 1440
gagcttgcag tgagccgaga tggctccact gcactccagc ctgggcgaca cagcgagact 1500
ccgtctcaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa 1544

<210> 215
<211> 1762
<212> DNA

<213> Homo sapiens

<400> 215
catgagccac tgcacccagc cgatactact atatccccat tttacagatg agcacatggg 60
caaattgagg gtaaggcact gacccatgat catacagctg agaagtggca aaggcaggat 120
ttgaacctag aacctctggc tccacacact agtaatctaa accactctcc ctacaataca 180
acatacgtgg taaagatgtg tggtgggcac gcaatcaacg taggtccctt cacagttgct 240
gggagaggca ggaatttgca gttcctccgc gttctcctcc tccgctgccc acctgtcctg 300
ggtcattcct gcagcctgcc ctgccctgcc tggtctcacc ctccctctgc caacagaagt 360
ctgggcaggg ttttatgggc tctgataagg ccctggcagg gccgaagttc atgagcactt 420
cctctttgca ggagggcgta ggggaggggga cccaggtgat ttgggtcctg gctggtcacc 480
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agtcccagaa gaggagccct gtggaccctc ccctgccagc cactccctta ccctgggtat 600
aagagccacc accgcctgcc atccgccacc atctcccact cctgcagctc ttctcacagg 660
accagccact agcgcagcct cgagcgatgg cctatgtccc cgcaccgggc taccagccca 720
cctacaaccc gacgctgcct tactaccagc ccatcccggg cgggctcaac gtgggaatgt 780
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acaaggtggt cttcaacacg ttgcagggcg ggaagtgggg cagcgaggag aggaagagga 960
gcatgcccctt caaaaagggt gccgcctttg agctggtctt catagtcctg gctgagcact 1020
acaaggtggt ggtaaatgga aatcccttct atgagtacgg gcaccggctt cccctacaga 1080
tggtcaccca cctgcaagtg gatggggatc tgcaacttca atcaatcaac ttcatcggag 1140
gccagcccct ccggccccag ggacccccga tgatgccacc ttaccctggt cccggacatt 1200
gccatcaaca gctgaacagc ctgcccacca tggaaggacc cccaaccttc aacccgcctg 1260
tgccatattt cgggaggctg caaggagggc tcacagctcg aagaaccatc atcatcaagg 1320
gctatgtgcc tcccacaggc aagagctttg ctatcaactt caaggtgggc tcctcagggg 1380
acatagctct gcacattaat ccccgcatgg gcaacggtac cgtggtccgg aacagccttc 1440
tgaatggctc gtggggatcc gaggagaaga agatcaccca caacccattt ggtcccggac 1500
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agcacctctt tgactttgcc catcgcctct cggccttcca gagggtggac acattggaaa 1620
tccagggtga tgtcaccttg tcctatgtcc agatctaatc tattcctggg gccataactc 1680
atgggaaaac agaattatcc cctaggactc ctttctaagc ccctaataaa atgtctgagg 1740
gtgtctcatg aaaaaaaaaa aa 1762

<210> 216
<211> 253
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (236)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (238)
<223> n equals a,t,g, or c

<400> 216
gggtaaatga gtgccagggc cggcaagccc ccgctccccg ggctctcggg gtcgcgcgag 60

gatgcttggc acgtaccccg tgtacatact tcccgggcgc ccagcatgga aataaagcac 120
ccascrctgc cctgggcccc tgcgaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 180
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aaaggttccc tcg 253

<210> 217
<211> 511
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (471)
<223> n equals a,t,g, or c

<400> 217
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ggagctaagg ctggccctcc agctttccta gctctgtggt cccggggcgg gactccggac 420
accatcacca tgctmactgc ttactcagtg tgtttcctgc acacctgcca ngcttctggt 480
ctaggcaatg ggacgtagca gtgaagcaag a 511

<210> 218
<211> 2945
<212> DNA
<213> Homo sapiens

<400> 218
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<210> 219
<211> 445
<212> DNA
<213> Homo sapiens

<400> 219
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ttgtgtggaa ggactattgc taagaagcag gagacagact gaacccagtg ttggccacaa 240
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ccatcttgtt ggttttttgg taaaatgtgg caccccytcc agacctytta gctgtggaam 420
tgagrtattt tagcagggtc ccgtt 445

<210> 220
<211> 522
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (402)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (417)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (480)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (482)
<223> n equals a,t,g, or c

<400> 220
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ttgacaagtg aatgaagttc acatctggaa atcgttgaac atttttcgtt catggaactc 180
aatggctacg ttagtcgttt atgcttttca ctgttgtggt aggggctttg gaagtaaatg 240
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tgccacctgg gcaatattgg ccgctaaggg tctctttatt cnccttactt ggacttnctt 420
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<210> 221
<211> 1516
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1493)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1497)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1508)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1509)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1516)
<223> n equals a,t,g, or c

<400> 221
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cgatggggat ggaagaggag atgcctgtga tgatgacatg gatggagatg gaataaaaaa 180
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tgtgggggat gcctgtgaca gttgtcctga tgtcagcaac cctaaccagt ctgatgtgga 300
taatgatctg gttggggact cctgtgacac caatcaggac agtgatggag atgggcacca 360
ggacagcaca gacaactgcc ccaccgtcat taacagtgcc cagctggaca ccgataagga 420
tggaattggt gacgagtgtg atgatgatga tgacaatgat ggtatcccag acctggtgcc 480
ccctggacca gacaactgcc ggctggtccc caacccagcc caggaggata gcaacagcga 540
cggagtggga gacatctgtg agtctgactt tgaccaggac caggtcatcg atcggatcga 600
cgtctgccca gagaacgcag aggtcaccct gaccgacttc agggcttacc agaccgtggt 660
cctggatcct gaaggggatg cccagatcga tcccaactgg gtggtcctga accagggcat 720
ggagattgta cagaccatga acagtgatcc tggcctggca gtggggtaca cagcttttaa 780
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tatatatttt aacttcaatt ttctttagct tttaccaacc caaatatatc aaaacgtttt 1440
atgtgaatgt ggcaataaag gagaagagat catttttaaa aaaaaaaaaa aanttcnggg 1500
gggcccgnnc caattn 1516

<210> 222
<211> 1387
<212> DNA
<213> Homo sapiens

<400> 222
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tcagctgctg tcgtcccagg gtggagccca ctgctacttc aggaggggcc tgctcaggtg 180
tagttaccac aggtgatggc tgagttcaga aacaacccag gggaagtgga aggaagaaag 240
gcaaaaagca tgaaggaaca gacaactggg aagaaccagg acaatcctgt gattgatgaa 300
atagacttcc ttgaagcttt taaaaatatt cagccctcat cgtttcgaag cgtcattgga 360

ttaatggata tcaagcctgt tgactgggag gagattggtg gccttgaaga tgtaaaactg 420
aagttaaaac agagcattga gtggcctctg aaattccctt gggaatttgt tagaatgggc 480
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gccagcaaga caggatgtga tgttcaagaa cgagttcttt ctgttctcct gaatgaatta 780
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acaaaac 1387

<210> 223
<211> 1506
<212> DNA
<213> Homo sapiens

<400> 223
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catcaaggag ctttatggag cttttgcttt ttctgccaac ttcacagatt ctgttacaac 600
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aaaaaa 1506

<210> 224
<211> 896
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (18)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (40)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (45)
<223> n equals a,t,g, or c

<400> 224
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ttaatgtgtt tgcaatagtc ttattaaaat aaatgttttt taaaaaaaaa aaaaaaaaaa 840
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<210> 225
<211> 127
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (94)
<223> n equals a,t,g, or c

<400> 225
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atgagat 127

<210> 226
<211> 1949
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1466)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1540)
<223> n equals a,t,g, or c

<400> 226
ctgagaggca ggtagctgcg gcgcagggct gacggcggcg agtccacgtg ctccccgcgg 60
ccggttgaaa ccgttggcgg gcgctggctg agaggcaatg tttgctgtct tccattggag 120
tgactgaatt tctacatgac ggctttttga caagacttaa aacctgtctt ggatagagaa 180
tatttagcca tttacctaaa aatggtattt tttacatgca atgcatgtgg tgaatcagtg 240
aagaaaatac aagtggaaaa gcatgtgtct gtttgcagaa actgtgaatg cctttcttgc 300
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cagcaggcgt ggattcagaa aattagtgaa ttaataaaga gacccaatgt cagcccccaaa 480
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gaaaaaaaaa aaaaaaaaaa aaaaaaaaa 1949

<210> 227
<211> 1179
<212> DNA
<213> Homo sapiens

<400> 227
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cataaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaa 1179

<210> 228
<211> 1958
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (374)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (377)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1244)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1300)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1311)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1327)
<223> n equals a,t,g, or c

<400> 228
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gtcctgcagg ctgtaatgca gtttaatcag agtgccattt tttttttgt tcaaatgatt 1860
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<210> 229
<211> 1751
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1741)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1742)
<223> n equals a,t,g, or c

<400> 229
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cacttgaaca aacctggtgg tctttggaaa taaatcacca ttagatttca cctggttatg 180
ctgcatccca taagttccaa atgaatcacc tgcttatcct attaacgaag catttaattc 240
acacacaaat gcttgaattt cccctgtata aatgtagtca tgcgattcaa cttttctaat 300
aagatttgtg aatgctgcat catgatgaaa atgtggatta actgtgggtt gcatgcctgt 360
tgttcatact tcagtgatgg tcacacacaa aacaagatga gttttactta ggtgaaacat 420
tattaaactg tactaacaat acagaaacat attctctttg tcgcttttta tcaccaaaac 480
tgaatggcaa atatgtcttg acattacttg gatgaactgt ggctagcaaa atggaattaa 540
cttagccact ataatttttt aaaacattaa agtttctaaa ttgtttttgg gggccgagta 600
acgcagagtc aataaaggtg gttatattgt aagcttttag atggtgctta agaattctta 660
tctttttaaa tagcagtatt ttttttttaa gaataaattg taaggagcaa ataaggcaga 720
atgccactct accctcaggt caattttatg gtatatgaaa atgccagtaa tatttgtgcc 780
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cattatcaga ctgactgaat gctttctgat ttccagtgag tgatctagtt ctacgtatta 1260
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agctttccta agtatatata aatgcatata tgtataaaat tgggaaaagt tacctcaata 1620
aaatcattgg gaaatcccaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1680
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1740
nnaaaaaggg c 1751

<210> 230
<211> 2153
<212> DNA
<213> Homo sapiens

<400> 230
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cccatatgtg gtctgtgagc caccccttaac actggttcct ttgctctttg atatgcctac 180
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acagatacta aaattcacac tcaagtccgt tattttatat aagtgtgaga tcttagataa 420
cctatgcata ctctcccata tactgtaaat aatctctaga tgatttgtaa tacctaacaa 480
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<210> 231
<211> 1360
<212> DNA
<213> Homo sapiens

<400> 231
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1360

<210> 232
<211> 1986
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (6)
<223> n equals a,t,g, or c

<400> 232
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gtacctgctg cttggcttca acctgctctt ctggctggct ggatcggccg tcattgcttt 120
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ggcaacagaa acaagttaag gaaaccaaaa tacttatata tacacaggac caaaataatg 1920
ttctttttat gcaaatcccc tgtggaaata aaattttcaa tgtttaaaaa aaaaaaaaaa 1980
aaaaaa 1986

<210> 233
<211> 705
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (108)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (680)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (696)
<223> n equals a,t,g, or c

<400> 233
ggattacatg tagttattga gaatcctttc gtaattcagt ggcttaatca tgtaatgtct 60
aaatattgtt gtacattagg atgtatacat gtaaattaaa gttacatntg tttagcatag 120
acaagcttaa cattgtagat gtttctcttc aaaaatcatc ttaaacattt gcatttggaa 180
ttgtgttaaa tagaatgtgt gaacactgta ttagtaaact tcatcacctt tctacttcct 240
tatagtttga acttttcagt ttttgtagtt cccaaacagt tgctcaattt agagcaaatt 300
aatttaacac ctgccaaaaa aaggctgctg ttggcttatc agttgtcttt aaattcaaat 360
gctcatgtga cttttatcac atcaaaaaat atttcattaa tgattcacct ttagctctga 420
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tatttgagaa ttttggtgaa aaatatttag ctgagggcag tatagaactt ataaaccaat 540
atattgatat ttttaaaaca tttttacata taagtaaact gccatctttg agcataacta 600
catttaaaaa taaagctgca tatttttaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660
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<210> 234
<211> 838
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (32)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (51)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (822)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (832)
<223> n equals a,t,g, or c

<400> 234
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gccctttcca tccattaaaa atgtccaagt tccaagtgat atgtgcccct aatatccacc 120
ttggatgttg gtgggttttt gaatttttgg gtggttaatc cagttttatt ttgaaaagac 180
gtacttgaat agttacagca tatgtttgaa caggaagtag gaacatgcat acacgaagaa 240
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taatgacatt actgtttgta gaatgacata tgcagatttt ctcataagca gtcattgtgt 360
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taattcgttg gttttgattc tcttattctc ttgtcttttc taaatgttaa caaaatatat 480
cttaacagat tacatgaaat ttaggaatta tttaaaagtt accattagct ctaaaattaa 540
gattcggatg ctttatttat agtaactgaa gctaataatg ttttatgttt tgattttttg 600
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tacactgctt ataatactaa tgtttacaga tatgtttctg tttataacca tataatacat 720
tggctttgtc atattagttt tttttgcaag tagttatgta aaagagatag ataataaaat 780
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<210> 235
<211> 1410
<212> DNA
<213> Homo sapiens

<400> 235
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gtgtgagcct gaatttggca atgacaaggc cagggagccg agcgtgggtg gcaggtggcg 180
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<210> 236
<211> 422
<212> DNA
<213> Homo sapiens

<400> 236
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tttctgccac tcactggtag cctggtagat ttgtagcaac tgttgcagcg cgccaatgcg 180
gaagtcagtt tcatcggtca gctgattgaa catgtcttcc gcgcggtcat ataacccggc 240
ggccatgtaa tcacgcccca gttgttgaat cgccaacaga cgctgttcat aggtcagcga 300
ggcgctttcc attagggtct gatggatgcg aatagcgcgg ttcaacttcg ccacggaacg 360
ggaacaggtt ttccgagcgt aaggtgggct tcaacggtgc ccgttattcc tgttttaagc 420
at 422

<210> 237
<211> 351
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (253)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (322)
<223> n equals a,t,g, or c

<400> 237
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cgttacgtta gaaaaatttc gttgcgtgct gaaagcgctt ttacctgtgt tgtatgattt 180
aaccttatga aaatggacag tatttccagt tttacaagtg aggaaagaag attaagaaac 240
ttgcctccgc cangcgtggt ggttcactcc ctgtaatccc agcactttcg gcggccgaag 300
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<210> 238
<211> 2682
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (647)
<223> n equals a,t,g, or c

<400> 238
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tagacagact atgctctttt ctgccaccca aactcgaaaa gttgaagacc tggcaaggat 180
ttctctgaaa aaggagccat tgtatgttgg cgttgatgat gataaagcga atgcaacagt 240
ggatggtctt gaacagaaga accgaaagaa gaagcttatg gtcttctttt catcttgtat 300
gtctgtgaaa taccactatg agttgctgaa ctacattgat ttgcccgtct tggccattca 360
tggaaagcaa aagcaaaata agcgtacaac cacattcttc cagttctgca atgcagattc 420
gggaacacta ttgtgtacgg atgtggcagc gagaggacta gacattcctg aagtcgactg 480
gattgttcag tatgaccctc cggatgaccc taaggaatat attcatcgtg tgggtagaac 540
agccagaggc ytaaatggga gagggcatgc cttgctcatt ttgcgcccag aagaattggg 600
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ctaaaatttc tgacattcag tctcagcttg agaaattgat tgaaaagaat tactttcttc 720
ataagtcagc ccaggaagca tataagtcat acatacgagc ctatgattcc cattctctga 780
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gacaaaaaca aagggaagaa tatttaatta ctgagcagaa gtaaatactg ttggtatttt 2520
gtacataatc taatttttat atgcatgtty atgcttttta atttttttat caaaaattaa 2580
gtcatctacc tactacttgt aaccagcttg tttcataaca tgttattttc ctgtgtcatt 2640
aaataattac ttcaatgttg aaaaaaaaa aaaaaaaaa aa 2682

<210> 239
<211> 2254
<212> DNA
<213> Homo sapiens

<400> 239
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tcaaatccac aatatgctgt ataataccgg ttttactata taatctattt tagacatagc 180
tgtttagaac tagagtgtgc tatttttgtg tttttctgat gtgtggtgct agacaagtta 240
cttttgtgaa caacaaaaat tatccctttt attcctagac aataccacct ttgggtcttg 300
ttaatttcac tgagtataac tatatatttg tatatatata catatatata tatatctacc 360
tatgcccaac tggcagctgt atcagagtgc tggatttggg acatgctttt ctctttaaat 420
acataatatc attatataaa ttattctaga gtgtatttaa ttaggataaa attacttcct 480
tagtatggat atttgacatc tatagggtga atttgtttat aaatatggct atatggaaac 540
ttattagcat ttactttatg tttgctactt ggctttacag catatctcct aagctgaaaa 600
ataatttgcc aggccttcaa gatcctaaag aaacttgttt aatggagtaa tatacttttt 660
tttcttatta aggaattgta ttactggcac ctaacacagt tgtattctta gctcctatta 720
tagataatgg gcatttacat aaaatatcct agatggcttg atggcagaat aaacctttcc 780
cctcctacct gagtcatgag aaggatggag acgtcctctg ccataacatg ggccataaag 840
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acacaaattt cacaaacttc tgtttgagta aacaaactca gccttctgta aatatacatg 1740
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tgtaaaaact ccttttctgc cacactaaaa atgcaagcca tttatgggaa tcctaaaact 1860
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tattgagtcc tgaatttaaa aaaaaaatat tttgattcat tttgtaaata caagctgtac 2040
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ctaatggaaa aaaaaaaaaa aaaaaaaact cgag 2254

<210> 240
<211> 1057
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (958)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (966)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1035)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1053)
<223> n equals a,t,g, or c

<400> 240
ttaactcaaa ctctaaagtc ttgagtgttt caaagtcagt cgttacctgt ttaaaagcct 60
cagcctttag cttattcctc cttcaataca cgggaccttt ggttaatttg gggcaggaaa 120
actcttaaag taatctctct tgggcagagg ccttattgca ccagagggaa aaagtatata 180
cttcatttgc tgttactcca gttatgcctt aaattcattt gcttggtaat cctatcaacg 240
rgcactaact tcttagtata ctttaaacac ttagttgggt aacactgaga ttttgttgtc 300
ctttattttt tgctgagatg gagtcagtca gatgttagtc atagctaaca ccgaatttgt 360
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aactgtaagt tctaggtaga ctaattggga gcagacacgg agttttagat gccttagcca 540
aacccagcag aaacctttca cacagccact catcgtaaga aacgcagatt tttctcttct 600
catgcttgtc tctggttccc tgcatttgta gtgacagaac tttcactagc aggatataaa 660
gaaagtaatt atgcttggag tccctcttta ctgggtttga gttaggtgca taacatggaa 720
aggagtggtg ccttcaaatg aatgtgacca ctccgtattg tggagtgact tccctagggc 780
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gccgtcttcc ttctggctta gcaggtgctg cagctgtact ctcgactcct gtctgtgnag 960
cgtganyagg gaaaatgagg agtggagtct atttccaaaa aaaaatgtgg atggagtttt 1020
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<210> 241
<211> 498
<212> DNA
<213> Homo sapiens

<220>

<221> misc feature
<222> (493)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (496)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (497)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (498)
<223> n equals a,t,g, or c

<400> 241
gagttgatcc tgagatgaag gtggagcgtt acaagcgcac ctttgaccaa aatgaggagc 60
tagggctcaa tgacatgaag acagagggct atgaggcagg cctggctccg caacggtagc 120
agtgggtggc tcaagggcca gcctccagcg ctgctctttc tgtaggttat ttattagtat 180
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gcctattgtg ttacttgacc ttattttgga agttttgaat tggcctagga ggaaacccag 360
aaatgaacca ggggtatgtc atcacttttt tcatatcaag tcctcaccct ccttccacat 420
aatgctctat cctctaargt tggaactctg aarttggaga argtggaata aagttacacc 480
tggaaaaaaa aanaannn 498

<210> 242
<211> 1784
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1739)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1777)
<223> n equals a,t,g, or c

<400> 242
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gcagatcatt ccccctgctg gctacttctc ccaagtggca gagcacatcc gcaaggccgg 180
aggggtcttt gttgcmgatg agatccaggt tggctttggc cgggtaggca agcacttctg 240
ggccttccag ctccagggaa aagacttcgt ccctgacatc gtcaccatgg gcaagtccat 300

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ttgaaagcac aactgaccct ggatttaagc tggccaggac cctgggagat ctttggaang 1740
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<210> 243
<211> 936
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (840)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (854)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (865)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (905)
<223> n equals a,t,g, or c

<400> 243
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gtagtcattt caacaggatt aactataatc tataattgat agattattga gtgacacaca 120
gcgtgatgct gggcaggccc caagctgaaa agcatctcct ccaacttact ttattcttag 180
caattcattc ctttggtttg aaaattcttc agcatcttca agagtccttt actaatgsat 240
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cctttgtaaa tacaaggcat agtctctgcc cttcccccag attgccagaa gagtgggata 720
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tgtgatagtg aagaatgtgg gggagtgttg tgagggctag gcgaagcggc ccggccttgn 840
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aaaanaaaaa caattttagc tggggcacaa tggctc 936

<210> 244
<211> 1381
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1348)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1349)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1350)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1358)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1359)
<223> n equals a,t,g, or c

<400> 244
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agagcaaaat cttgaaagtc attcgcaaaa acattgttaa gaagtgcctt gagctcttct 120

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ctgagctggc agaagacaag gagaattaca agaaattcta tgaggcattc tctaaaaatc 180
tcaagcttgg aatccacgaa gactccacta accgccgccg cctgtctgag ctgctgcgct 240
atcatacctc ccagtctgga gatgagatga catctctgtc agagtatgtt tctcgcatga 300
aggagacaca gaagtccatc tattacatca ctggtgagag caaagagcag gtggccaact 360
cagcttttgt ggagcgagtg cggaaacggg gcttcgaggt ggtatatatg accgagccca 420
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c                                                                 1381
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<210> 245
<211> 779
<212> DNA
<213> Homo sapiens

<220>
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<222> (10)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (39)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (41)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (650)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (669)

<223> n equals a,t,g, or c

<400> 245
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ctggctcttt acatatattg gatggtcctc atggcaaaac ttctcaattc cttaattagt 120
catgtctcag cttcaaggat atcagacagg aatgaaacac acttgaaaat gagattgacc 180
tggagatttt ttttccctaa tctctcatac cttaattgga aaaataatca attaattcta 240
tgttaattag grtatacaaa gttcaccctc cttgmaagtg actagggcaa gccctgaaga 300
tcttcctcac ctccttttat ctttctataa ccttgtctcc tccagcacca cagggaagac 360
aatcacagtg ggtcaagagc gaccctcttt cacgtgggct ctgcatgacc tctgagacct 420
gcttatgatc agtgcaatga agttagaagt aactgatgat tgggagcctt tgcagatagc 480
tgggcaaatg ggtgatttac ttatccccat tctaaatgga gtgagctctc tttgaggcta 540
agcaaggagg cgttgtatgc tagtttctag actttgcctg gagacccctt tggaaatctg 600
tcttcttttt aaactcactt aatatgcctt aatcatctgk gtgtaatggn agtcatccgc 660
tcctcaatnt aaccctyctm ccctggggct ttggctgtcc tcaatgagag tttcatgcag 720
aatggaaaat cctctatatg tacaatctct ctccccctca tttctcttcc tcctcacct 779

<210> 246
<211> 1231
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (795)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1219)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1229)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1230)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1231)
<223> n equals a,t,g, or c

<400> 246
ccacgcgtcc ggaagaaggc ctaattccta acctgggacc cagagagaga cataagatat 60
ccagagagat atgcaccaag aaactgcaat ttatacaaag acagtcagaa agcagctgaa 120
gacagaatga gagagaaact aagtaaaaga aacttgatgc ctccaaaatg aagagtatgc 180

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ctcatttcca tatgtgaact gaaaagctct ccacttttga aataaaggct tactatagag 240
cagccctggt aatagaacta caagacttat aataacttcc tgtttgagtt gaaatgaaaa 300
ctcataaaga atctatgcta ttaacccccт aatttatact tttgtattct tttatgttgt 360
attttgtatt ttatgttgga cttctttttt aaaattttgt atttattttt aattgaaaaa 420
taattgtgta tacttattgt tgtacaacat gatgttttga tatatgtata tgttgtagaa 480
tgactaaatc aagctagtta acatatgcat tacctcctat acttatcatt tatttgtggt 540
gagaacattt aaaatctact ctgttagcaa ttttgaagta tagaatacac tatgtcaact 600
ataatcatgg tgttgtacag taggtctaaa tgtattcatt tctcctatct aactgaaaat 660
ttgtatcttt tgaccaacat ctccctggtc cctccatctc ctcccctggt aactaccatt 720
attttttttt cttttttta aaaaaaagct tttagtttcg agggtacacg tgtaggtttg 780
ttatatagat aaacncaagt catgggactg tgttgtacag attattttgt cgtccacgta 840
ctaagcctag tgcccaatag ttattttttc tgctcttctc cctcctccta ccctctgcca 900
tcaagttggc ctaatgtcta ttgttccctt ctttgtaaca accactctaa tctctgcttc 960
taagggttcc tatgtctgac ttctttccct tgattttgtg agattcatcc acgttgtgta 1020
tgcagcagta gtttatttat tttcattatt ggatagtatt cctttgtgtg aacataaatt 1080
gctgatggca gatgtttgaa ttgtttccag tttttgagta ttatgaataa tgctgttgtg 1140
aacaaaaaaa aaaaaaaaaa aaaaaaaggg cggccgctct agaggatcca agcttgcgta 1200
cgcgtgcatg aaacgtcana agggtcttnn n                                1231
```

<210> 247
<211> 851
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (817)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (834)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (842)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (844)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (849)
<223> n equals a,t,g, or c

<400> 247

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gcggacgcgt gggcgtggat cggctggagc ggggccgccg ccggctgcag caggagctgg 60
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acgacgccac catggacctg gagcagcagc ggcagcttgt gagcaccctg gagaagaagc 120
agcgcaagtt tgaccagctt ctggcagagg agaaggcagc tgtacttcgg gcagtggagg 180
aacgtgagcg ggccgaggca gagggccggg agcgtgaggc tcgggccctg tcactgacac 240
gggcactgga ggargagcag gaggcacgtg aggagctgga gcggcagaac cgggccctgc 300
ggctgagctg gaggcactgc tgagcagcaa ggatgacgtc ggcaagagcg tgcatgarct 360
ggaacgagcc tgccgggtag cagaacaggc agccaatgat ctgcgagcac aggtgacaga 420
actggaggat gagctgacag cggccgagga tgccaagctg cgtctggagg tgactgtgca 480
ggctctcaag actcagcatg agcgtgacct gcagggccgt gatgaggctg gtgaagagag 540
gcggaggcag ctggccaagc agctgagaga tgcagaggtg gagcgggatg aggagcggaa 600
gcagcgcact ctggccgtgg ctgcccgcaa gaagctggag ggagagctgg aggagctgaa 660
ggctcagatg gcctctgccg gccagggcaa ggaggaggcg gtgaagcagc ttcgcaagat 720
gcaggcccag atgaaggagc tatggcggga ggtggaggag acacgcacct tccgggagga 780
gatcttctcc cagaatcggg aaagtgaaaa gcgcctnaag ggcctgaagc tgangtgctg 840
cngntgcang a 851

<210> 248
<211> 1802
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1680)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1747)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1757)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1800)
<223> n equals a,t,g, or c

<400> 248
acgcgtccgc ttccatctgc tctggaatta aatatgcatt tcaggtgatt ggagagctac 60
attcccaact cgatggatcc gaagtactgc tgctgactga tggggaggat aacactgcaa 120
gttcttgtat tgatgaagtg aaacaaagtg gggccattgt tcattttatt gctttgggaa 180
gagctgctga tgaagcagta atagagatga gcaagataac aggaggaagt catttttatg 240
tttcagatga agctcagaac aatggcctca ttgatgcttt tggggctytt acatcaggaa 300
atactgatct ctccsagaag tcccttcagc tcgaaagtaa gggattaaca ctgaatagta 360
atgcctggat gaacgacact gtcataattg atagtacagt gggaaaggac acgttctttc 420
tcatcacatg gaacagtctg cctcccagta tttctctytg ggatcccagt ggaacaataa 480
tggaaaattt cacagtggat gcaacttcca aaatggccta tctyagtatt ccaggaactg 540
saaaggtggg cacttgggca tacaatctty aagccaaagc gamcccagaa acmttaacta 600

ttacagtwac ttctcgagca kcaaaattct tctgtgcctc caatcacagt gaatgctaaa 660
atgaataagg acgtaaacag tttccccagc ccaatgattg tttacgcaga aattctacaa 720
ggatatgtac ctgttcttgg agccaatgtg actgctttca ttgaatcaca gaatggacat 780
acagaagttt tggaactttt ggataatggt gcaggcgctg attctttcaa gaatgatgga 840
gtctactcca ggtattttac agcatataca gaaaatggca gatatagctt aaaagttcgg 900
gctcatggag gagcaaacac tgccaggcta aaattacggc ctccactgaa tagagccgcg 960
tacataccag gctgggtagt gaacggggaa attgaagcaa acccgccaag acctgaaatt 1020
gatgaggata ctcagaccac cttggaggat ttcagccgaa cagcatccgg aggtkcattt 1080
gtggtatcac aagtcccaag ccttccttgc ctgaccaata cccaccaagt caaatcacag 1140
accttgatgc cacagttcat gaggataaga ttattcttac atggacagca ccaggagata 1200
attttgatgt tggaaaagtt caacgktata tyataagaat aagtgcaagt attcttgatc 1260
taagagacag ttttgatgat gctcttcaag taaatactac tgatctgtca ccaaaggagg 1320
ccaactccaa ggaaagcttt gcatttaaac cagaaaatat ctcagaagaa aatgcaaccc 1380
acatatttat tgccattaaa agtatagata aaagcaattt gacatcaaaa gtatccaaca 1440
ttgcacaagt aactttgytt atccctcaag caaatcctga tgacattgat cctactccta 1500
ctcctactcc tactcctgat aaaagtcata attctggagt taatatttct acgctggtat 1560
tgtctgtgat tgggtctgtt gkaattgkta actttatttt aagtaccacc atttgaacct 1620
taacgaagaa aaaaatcttc aagtagacct agaagagagt tttaaaaaac aaaacaatgn 1680
aagtaaagga tatttctgaa tcttaaaatt catcccatgt gtgatcataa actcataaaa 1740
ataattntaa gatgtcngga aaaggatact ttgattaaaa taaaaacact catggatatn 1800
ta 1802

<210> 249
<211> 444
<212> DNA
<213> Homo sapiens

<400> 249
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tgccccagaa cttcactggg cttccttcca taactatgga tctgtgagca tcactttaat 120
ttcagagtgt ggaagacacc ttaataagaa tcatgaatca cattttacaa atcaggatac 180
acaggatgta aggttaagtg acctgtccta tcagggccac aaagccagtt aaacttcttt 240
attaactgag tcacttaaaa atcatttatt taaaaaccta ttttgttcca ggaactattc 300
tgggtactgg aaatraaaac agtggagaca gagagagggg aaataaaaaa caagacaaaa 360
atgattgctt tkgtggagtt tatatattcc actggargaa ggtagatsat aaataaaagt 420
gaaaaagtac attatwaggt ggga 444

<210> 250
<211> 1746
<212> DNA
<213> Homo sapiens

<400> 250
ggcatcagta aggtctgtat ttaaatgtgg atgtagacat cataattacc aagacaagaa 60
attgttttga gaaattctct gatgtttttc ttcttcaggt ttcacgtgcc acgatcatgg 120
tgccacggta ctgcagtatg cacccaaaca gcaactccta atctcggggg gtaggaaaag 180
acacgtctgc atttttgaca tcargcaaag gcagctcatt cacacgttcc aggcccatga 240
ctcagctatt aaggctctgg ccttggatcc ctatgaggaa tattttacca caggttcagc 300
agaaggtaac ataaaggttt ggagattgac aggccatggc ctaattcatt catttaaaag 360
tgaacatgct aagcagtcca tatttcgaaa cattggggct ggagtcatgc agattgacat 420
catccagggc aatcggctct tctcctgtgg tgcagatggc acgctgaaaa ccagggtttt 480

gcccaatgct tttaacatcc ctaacagaat tcttgacatt ctataaagat tggggtttta 540
tttttatata catttcagtt aaaaggcaca ctacagtcat cactaggcaa ttctgctttc 600
taagcagttg tattgaaaac agagaatctc tgtgtagaat ttgaatatga cccaagctga 660
gtattatcta aacaggttgg tggaatgaat gcgcatgtac cttattatgc tgacatacta 720
aaaaaaataa aacctagtat tgtatgaagg atagctattc tttacagcat ttagcaaacc 780
tgattcagaa aacatttgag attagcaaat tagtaacttg aaataatgaa aaggacgttt 840
ataccaaatt aaggaagaaa atgttgctga tttgggtttt tcttcctgtt cttaccactg 900
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gttaggaatg tactatgtga acatgacata tttgtagtta accaaacaca ccttcttagt 1260
ccagtttagt actttttctt ttcgtgtatt caaggttaaa cacccaaaca tttaaggata 1320
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gtggccagtt aatagttgat gagattggtg acattattta ttgccacagc ctattgtata 1440
aactatgcag agttaaatat ttgcttgtaa aatattagcc aatgttgtca ttattttgat 1500
gtatttcctt ggttatgacc aaaaatatgt tgagatactg aaactaatgt ctgtgtgttt 1560
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aatagtaaat acaatggcat aaaagtaact ttctctgaag atgtgatgtt caggctgtga 1680
aatatatatg taaaagaaaa ataaatgtta tttgttagaa aaaaaaaaaa aaaaaaaaaa 1740
ctcgta 1746

<210> 251
<211> 1935
<212> DNA
<213> Homo sapiens

<400> 251
gaattcggca cgagggagca ttgcccgtca gacagcaact cagagaataa ccagagaaca 60
accagattga aacaatggag gatctttgtg tggcaaacac actctttgcc ctcaatttat 120
tcaagcatct ggcaaaagca agccccaccc agaacctctt cctctcccca tggagcatct 180
cgtccaccat ggccatggtc tacatgggct ccaggggcag caccgaagac cagatggcca 240
aggtgcttca gtttaatgaa gtgggagcca atgcagttac ccccatgact ccagagaact 300
ttaccagctg tgggttcatg cagcagatcc agaagggtag ttatcctgat gcgattttgc 360
aggcacaagc tgcagataaa atccattcat ccttccgctc tctcagctct gcaatcaatg 420
catccacagg gaattattta ctggaaagtg tcaataagct gtttggtgag aagtctgcga 480
gcttccggga agaatatatt cgactctgtc agaaatatta ctcctcagaa ccccaggcag 540
tagacttcct agaatgtgca gaagaagcta gaaaaaagat taattcctgg gtcaagactc 600
aaaccaaagg caaaatccca aacttgttac ctgaaggttc tgtagatggg gataccagga 660
tggtcctggt gaatgctgtc tacttcaaag gaaagtggaa aactccattt gagaagaaac 720
taaatgggct ttatcctttc cgtgtaaact cggctcagcg cacacctgta cagatgatgt 780
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ccactggctt ggagctgctg gaaagtgaaa taacctatga caaactcaac aagtggacca 960
gcaaagacaa aatggctgaa gatgaagttg aggtatacat accccagttc aaattagaag 1020
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accaagccat ggtggatgtg aatgaggagg gcactgaagc agccgctggc acaggaggtg 1200
ttatgacagg gagaactgga catggaggcc cacagtttgt ggcagatcat ccttttcttt 1260
ttcttattat gcataagata accaactgca ttttattttt cggcagattt tcctcaccct 1320

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gctatttcaa attgccaaaa atttagagat gttttctaca tatttctgct cttctgaaca 1440
acttctgcta cccactaaat aaaaacacag aaataattag acaattgtct attataacat 1500
gacaacccta ttaatcattt ggtcttctaa aatgggatca tgcccattta gattttcctt 1560
actatcagtt tatttttata acattaactt ttactttgtt atttattatt ttatataatg 1620
gtgagttttt aaattattgc tcactgccta tttaatgtag ctaataaagt tatagaagca 1680
gatgatctgt taatttccta tctaataaat gcctttaatt gttctcataa tgaagaataa 1740
gtaggtatcc ctccatgccc ttctgtaata aatatctgga aaaaacatta aacaataggc 1800
aaatatatgt tatgtgcatt tctagaaata cataacacat atatatgtct gtatcttata 1860
ttcaattgca agtatataat aaataaacct gcttccaaac aacaaaaaaa aaaaaaaaaa 1920
aactttgagg ggggg                                                  1935
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<210> 252
<211> 1919
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (253)
<223> n equals a,t,g, or c

<400> 252

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tgcatatccc accataatag ggaaattaat aattgtatta agtggttgaa aaaaaggggg 180
aggatgttca ctcactgttc cctgtgtagt atcctgcaaa tgcatgaatg gtgaactccc 240
catgtcagca ttnttgtgcc catttattta gtacccagac atagtgctgg tctcacagct 300
taatatttgg taatgaataa attctgctag tggtatatgt tgatctgaac ttacaatgat 360
gggatataga attggcagag tggcagatgt tcacaattgt ctacaagtag atgtgctaga 420
caatggaagg atgcaggcca acctctttga ttacaattga gattcatgtg actattgagc 480
cctggaaatg tagcttgtcc aaattgagat gtgctgtcag tataaaatac ataccagatt 540
ttaaagatgt accaaaaaat gtaaactatc tcaattttta tattggtgaa atcaatatgt 600
cttggtatag tggcttaaat aaaacaattt tagcctttct cagtttattt ttctgcaaaa 660
agattaaaaa ttgtacatga agctcatgtt aactttcttt tggtcagtgc tattttaaag 720
gaagtatgag ttgaaaaaaa attgaaataa actatatcat attactagga cttaatatag 780
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aactttgttc attgtttttt ttgtttgtct ttctgacaca gaaagactga tgatggtgtc 1200
cactatgtat tcttcaaaac atttggcaca tgctgcacta acctagtcta tcttttctat 1260
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gttgttggaa gagcagcatt ttgacccttg gagaagaaaa actagctgtg gcattccagg 1560
tggagaacct gacagaggac taagaagtta tctaatgtaa aagacctcag gcaccacctt 1620
cgcataaact ttttccagac aaggctaaat gtgcatgctt cataaccata attcttattt 1680
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ttctttaata aatatttttc tacttgtaac actgtgcatt atttcaaact gtttacctgt 1740
ttgtaaagct tgtctcttaa tcaaatttgt cttgaccaaa taagtttcct gagggctgga 1800
attatgcctt aactatatct atagtattta acagtgaatc ctttgtataa tgaaagcatc 1860
aacagataat tttaaattga taaataaaaa gcacagtttc aaatggtaaa aaaaaaaaa 1919

<210> 253
<211> 2468
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (2076)
<223> n equals a,t,g, or c

<400> 253
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aggacaggag gtggccatta agcagatgaa tcttcagcag cagcccaaga aagagctgat 120
tattaatgag atcctggtca tgagggaaaa caagaaccca aacattgtga attacttgga 180
cagttacctc gtgggagatg agctgtgggt tgttatggaa tacttggctg gaggctcctt 240
gacagatgtg gtgacagaaa cttgcatgga tgaaggccaa attgcagctg tgtgccgtga 300
gtktctgcag gctctggagt tcttgcattc gaaccagata accccagagc agagcaaacg 360
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tgggcccaag gttgacatct ggtccctggg catcatggcc atcgaaatga ttgaagggga 480
gcctccatac ctcaatgaaa accctctgag agccttgtac ctcattgcca ccaatgggac 540
cccagaactt cagaacccag agaagctgtc agctatcttc cgggactttc tgaaccgctg 600
tctcgagatg gatgtggaga agagaggttc agctaaagag ctgctacagc atcaattcct 660
gaagattgcc aagcccctct ccagcctcac tccactgatt gctgcagcta aggaggcaac 720
aaagaacaat cactaaaacc acactcaccc cagcctcatt gtgccaagcc ttctgtgaga 780
taaatgcaca tttcagaaat tccaactcct gatgccctct tctccttgcc ttgcttctcc 840
catttcctga tctagcactc ctcaagactt tgatccttgg aaaccgtgtg tccagcattg 900
aagagaactg caactgaatg actaatcaga tgatggccat ttctaaataa ggaatttcct 960
cccaattcat ggatatgagg gtggtttatg attaagggtt tatataaata aatgtttcta 1020
gtcttccgtg tgtcaaaatc ctcacctcct tcataaccat ctcccacaat taattcttga 1080
ctatataaat ttatggtttg ataatattat caatttgtaa tcaattgaga tttctttagt 1140
gcttgctttt ctgtgactca actgcccaga cacctcattg tacttgaaaa ctggaacagc 1200
ttgggaatgc catggggttt gataatctgc cagggacatg aagaggctca gcttcctgga 1260
ccatgacttt ggctcagctg atcctgacat gggagaacaa ccacattttt ctttgtgtgt 1320
gcttctagca gctgttcggg aggaccttga cccaayagtg ttcccatgct gtttcttgtg 1380
aaatgctctc ggctatgtag cagcttttga ttccctgcat accctaggct gctgccccta 1440
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gttgagaagt cggggaaaat ggtgactact tttagagcaa ggctgggcat cagcacctgt 1560
ccagctctac ttgtgtgatg tttcaggaac tcagcccctt tttctgccta ggataaggag 1620
ctgaaagatt aacttggatc ttctaatggt ccaaatcttt tggtcacaat aaagagtctc 1680
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<210> 254
<211> 2861
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (2861)
<223> n equals a,t,g, or c

<400> 254
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<212> DNA
<213> Homo sapiens

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<222> (107)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (709)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (722)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (732)
<223> n equals a,t,g, or c

<400> 255
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tcgtgcccag gagcgtctgg caacagcttt gcagaagctg gaggaagctg ataaggcagc 660
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<210> 256
<211> 1394
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1238)
<223> n equals a,t,g, or c

<400> 256
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gagagcattt tccgtgaagt ttgaggtcca ggctccacgc tggggcaacc cccgtgcgct 480
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acaccaaaaa aaaa 1394

<210> 257
<211> 1329
<212> DNA
<213> Homo sapiens

<400> 257
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aaggtgcmct ccctgmtgac ctccaccayc aacggcatta agraagtcct gaaraagcac 180

artgatgact ttgagatgac gtcattctkg ttatccaaca cctgccacct tcttcactgt 240
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aaaaaaaaa 1329

<210> 258
<211> 2196
<212> DNA
<213> Homo sapiens

<400> 258
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ggctcccgag gtgaagagca tcgggggctg agggatggaa gggtctaaga cgtccaacaa 180
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<210> 259
<211> 567
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (236)
<223> n equals a,t,g, or c

<400> 259
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tatgaatgat ggaacccaaa atgaatg 567

<210> 260
<211> 950
<212> DNA
<213> Homo sapiens

<400> 260
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<210> 261
<211> 475
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (444)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (451)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (454)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (470)
<223> n equals a,t,g, or c

<400> 261
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<210> 262
<211> 1244
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1230)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1232)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1235)
<223> n equals a,t,g, or c

<400> 262
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tgagaaaaag gacatatgag tttttgcatt tattaatgaa acttcctttg aaaaactgct 540
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aagagctaat gttattttgc aaatgccata tattcaaaaa agctcaaaga taattttctt 720
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ttaatcttca agaaatcatg ctacacttaa cttctcctag aagctaatct ataccataat 840
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aaaaaaaaaa aaaaaaaaag gggcggccgn tntanaggat ccaa 1244

<210> 263
<211> 1132
<212> DNA
<213> Homo sapiens

<400> 263
cttccaactt ggtacctgtg gatatcatag aaagtgtagt ttcaaaggag atggacaaac 60
gatacctaca gtttgatatt aaggcctttg ttgaaaataa tcctgccatt aaatggtgtc 120
ctactccagg ctgtgacaga gcagtaagac taacgaaaca agggtcaaat acatctggat 180
ctgatacact cagcttccca ttgctgagag ctcctgctgt tgattgtgga aaaggacacc 240
tcttctgctg ggagtgcctt ggtgaagcac atgagccttg tgactgccaa acatggaaga 300
attggctgca aaaaataacc gaaatgaaac cagaagaact tgtgggagtt agtgaagcct 360
acgaggatgc cgccaattgt ctctggttat taactaactc caagccttgt gccaactgta 420
agtctccaat acagaagaat gaaggctgca atcacatgca gtgtgctaag tgcaagtatg 480
acttttgctg gatttgcctt gaagagtgga aaaaacatag ttcgtccact ggaggttatt 540
acagatgtac tcgctatgaa gtcattcaac acgtggagga gcaatccaag gaaatgactg 600

tggaggctga gaaaaaacac aaacgatttc aggaacttga cagatttatg cactattata 660
caagatttaa aaaccatgag catagttatc agctagaaca acgccttctt aaaacagcca 720
aagaaaagat ggagcaattg agcagagctc tcaaagaaac tgaaggaggc tgtccagata 780
ccactttcat tgaagatgca gttcatgtgc tcttaaaaac tcggcgcatt ctcaagtgtt 840
cttatccata tggatttttc ttggaaccta aaagcacaaa gaaagaaatt tttgaactaa 900
tgcaaacaga cctagaaatg gtcactgaag accttgccca gaaagtcaat aggccttacc 960
ttcgcacacc ccgccacaag atcatcaaag cagcatgcct tgtacagcag aagaggcaag 1020
aattcctggg catctgtggg ctcgggggag tagctcctgc agactcacca gaagcttcca 1080
aggcgcattt tgstggtggg aacatggggr ttggggrata tttwggggtt tt 1132

<210> 264
<211> 499
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (447)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (466)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (467)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (469)
<223> n equals a,t,g, or c

<400> 264
ggcacgagtg aagctgaagt actgcttcac ctgcaagatg ttccggccac cccgaacctc 60
acactgcagt gtctgcgaca actgtgtgga acgatttgac catcactgcc cctgggtggg 120
caactgtgtg gggagacgga actatcgctt cttctacgcg tttattctct ccctctcatt 180
cctgacggcc ttcatcttcg cctgtgtggt cacccacctg acgttgcgcg ctcagggaag 240
caacttcctc tccactctga aggagacacc agcaagcgtg ctgggagttg gtgatctgct 300
tcttctccat ctggtccatt ctgggcctct cagggtttca cacgtacctc gtcgcctcca 360
acctgactac taatgaagac atcaaaggtt cgttggtcca gcaagagggc ggtgagcctc 420
ttgtcaaccc tacagcataa agtattntca ccaatggcgg gtgggnntng ggccctaact 480
tccagctatt gacgggggg 499

<210> 265
<211> 735
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (648)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (713)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (730)
<223> n equals a,t,g, or c

<400> 265
ggagacacca ccattcctct cagcctgtgt ctgtctcaaa ggccccacct cacctcccct 60
aaaggcagcc gctgcagtcg ccacaccttt gcccctgctg cgatgaccct gtcgccactt 120
ctgctgttcc tgccaccgct gctgctgctg ctggacgtcc ccacggcggc ggtgcaggcg 180
tcccctctgc aagcgttaga cttctttggg aatgggccac cagttaacta caagacaggc 240
aatctatacc tgcgggggcc cctgaagaag tccaatgcac cgcttgtcaa tgtgaccctc 300
tactatgaag cactgtgcgg tggctgccga gccttcctga tccgggagct cttcccaaca 360
tggctgttgg tcatggagat cctcaatgtc acgctggtgc cctacggaaa cscacaggaa 420
caaawtktca ktggcaggtg ggagttcaag tgccagcatg gagaagagga gtgcaaattc 480
aacaaggtgg aggcctgcgt gttggatgaa cttgacatgg agctagcctt cctgaccatt 540
gtctgcatgg aagagtttga ggacatggag agaagtctgc cactatgctg cagctctacg 600
cccaggctgt cgcagaacta tcatgagtgt gcaatgggac gcggcatnag tcatcacgca 660
acgccacgac agatctctca gcacaaagat atgtcctggt acgcaatgga acntgagata 720
accagtctan ctgtt 735

<210> 266
<211> 851
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (834)
<223> n equals a,t,g, or c

<400> 266
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ccaggagcac agctgtgatg aacagtactt gtgtcagttc tgtgaacatg aaactaatga 120
tccagaagac ttgcatagcc atgtggtaaa tgagcatgca tgtaaattaa tagagttaag 180
tgataagtat aacaatggtg aacatggaca gtatagcctc ttaagcaaaa ttacctttga 240
caaatgtaaa aacttctttg tatgtcaagt atgtggtttt cggagtagac ttcacacaaa 300
tgttaacagg catgttgcta ttgaacatac aaaaattttt cctcatgttt gtgatgactg 360
tgggaaaggc ttttcaagta tgctagaata ttgcaagcat ttaaattcac atttatctga 420
agggatttat ttatgtcaat attgtgaata ttcaacagga caaattgaag atcttaaaat 480
tcatctagat ttcaagcatt cagctgactt gcctcataaa tgtagtgact gcttgatgag 540
gtttggaaat gaaagggaat taataagtca ccttccagtc catgagacaa cttgattatt 600

ctctttaact tacagaatgt tagtttaaaa taataaattc atcctttttt tggagatgat 660
taaatggatg attgtaaaca caacttatga aatctgcctt taacaagtaa ctttttttaaa 720
ttataaaatt ttattggcat tgctccattt tctgtatata aatatatctt taatgtggta 780
ttttcaaaaa aaaaaaaaaa aaaaaaatcc acgcggccgc gaattcccgg gtcnaacaag 840
ctcactaatc c 851

<210> 267
<211> 1257
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (51)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (118)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1213)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1217)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1238)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1245)
<223> n equals a,t,g, or c

<400> 267
tcccggtgtt tggtggatgt ggtggtcgcc aaagaagagt tagccattcc naccgcagat 60
tcaaattcga acaggccaaa gtttcagcct gtatattgcg cgcaatcatc agcggacncg 120
gtgatgaagt gatcgaactg gcgaaaacaa atggctaagg taaaaagggt ggcatttccg 180
tcataataag gacatgccat gattgattta cgcagtgata ccgttacccg accaagccgc 240
gccatgctcg aagcgatgat ggccgccccg gttggggacg acgtttacgg agacgaccct 300
accgttaatg ctctgcagga ctacgcagca gagctttccg gtaaagaagc cgccattttt 360
ctgcctaccg gcactcaggc caacctggtc gctctgctca gtcactgcga acgcggcgaa 420
gagtatattg tcggtcaggc cgcgcataac tatctgtttg aagccggtgg cgcggcggtg 480
ctgggcagta ttcaaccgca acccatagac gcggctgccg acggcacgct accgctggat 540

aaagtggcga tgaaaatcaa acccgacgat atccatttcg cccgcaccaa attactcagt 600
ctggaaaaca cccacaacgg caaagtgttg ccgcgggaat acctgaaaga agcatgggaa 660
tttacccgcg agcgcaatct ggcgctgcat gttgacggtg cgcgcatctt taatgccgtg 720
gtggcttacg gctgcgaact gaaagagatc acgcaatatt gtgattcgtt caccatttgc 780
ctgtcgaaag gtcttgggac gccagtcggt tcattactcg tcggtaatcg tgattacatt 840
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aacgctgcct ggatggcgga cagctgcgtg aarcargcgc ggatgtgatg cgtcaggaca 1020
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tctcgcgcga acaactggcg gaagtcgccg cccactggcg tgcattcctg gcgcgttaag 1200
gagagaaacg ttncgcnaag cattttagtt ctccgtgnca attgntacat tgtcaac 1257

<210> 268
<211> 1085
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1067)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1081)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1083)
<223> n equals a,t,g, or c

<400> 268
gcaaaatttt agcatctctc aataatcata ctttttctct ttaattatca acaaaatatt 60
ttcatgttaa gctatctctt gcattcctag aataactcta cttgatcatg atgttttttc 120
ttttaataat ggaattataa ataagtatac agtttttgta tgaaaatgtt tttatttctc 180
tggagcatgt acctatggat ggaattacta aatcatatgc tagttctgtg tttaactatt 240
tgaaggattg aaggagtgcc agattgtttt ccaaagtggc tgtaccattt tacattccta 300
cctgcagtgt atgaaggttt caatttctcc acatcctcac caatattatt atctgtcttt 360
ctgattgtag ccatcctagt gggtgtgaag tggatatctt gtgacttgga tttgattttc 420
cctgatggct aatgatattg aacatctatc tttctctgtg cttattggtc atttgtatat 480
tttctttgga gaaatgtcta ttccagatcc yttttctgtt tttaaaaaat arctttattg 540
aggtwtattt gacaaataaa aatttgktgt atatttaaaa tgtatttaaa agaaaattga 600
gagaaaggac tacagagccc cgaattaata ccaatagaag ggcaatgctt ttagattaaa 660
atgaaggtga cttaaacagc ttaaagttta gtttaaaagt tgtaggtgat taaaataatt 720
tgaaggcgat cttttaaaaa gagattaaac cgaaggtgat taaaagacct tgaaatccat 780
gacgcaggga gaattgcgtc atttaaagcc tagttaacgc atttactaaa cgcagacgaa 840
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gtggaaaact ggaagacaga agtacgggaa ggcgaagaaa agaatagaga agatagggaa 960
attagaagat aaaaacatac ttttagaaga aaaaagataa atttaaacct gaaaagtagg 1020

aagcaraara aaaaaaaaaa aaaaaaaaaa aaaaaagggc ggccgcnctg gggccccagc 1080
ntncg 1085

<210> 269
<211> 1315
<212> DNA
<213> Homo sapiens

<400> 269
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atgcggagcc gccagctaag cggcacgcca cagcagagga ggtggaggaa gaagagaggg 180
accggatccc aggccccgtt tgcaagggaa agtggaaaaa taaggaacgg attctcatct 240
tttcttccag aggaataaat tttagaacaa gacatttaat gcaggacttg agaatgttga 300
tgcctcattc taaagcagat actaaaatgg atcgtaagga taagctattt gtgattaacg 360
aggtttgtga aatgaagaac tgtaataaat gcatctattt tgaagctaag aaaaaacagg 420
atctctatat gtggctttca aattcacctc acggaccatc tgctaaattc cttgttcaaa 480
atattcatac cctcgctgaa ctgaagatga ctggaaactg tttgaaaggt tctcggcccc 540
ttttgtcttt tgaccctgct tttgatgaat taccacatta tgctttgkta aaagaactct 600
taattcagat ctttagtaca ccacggtatc atcccaaaag ccaaccattt gtggaccacg 660
tgtttacttt caccattttg gataatagga tatggtttcg gaactttcag atcatagaag 720
aagatgctgc tcttgtagaa ataggacctc gttttgtctt aaatctcata aagattttcc 780
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atgtgcaaaa actgagaaag aaagagccga agactcttct tccacatgat cccactgcag 960
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<210> 270
<211> 2959
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (2948)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2956)
<223> n equals a,t,g, or c

<400> 270
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atgccatcat gcaagttgca gtttgtggat cactgattgg ctggaggaat gttacacggc 120
tgctggtgtt ttccacagat gccgggtttc actttgctgg agatgggaaa cttggtggca 180

ttgttttacc aaatgatgga caatgtcacc tggaaaataa tatgtacaca atgagccatt 240
attatgatta tccttctatt gctcaccttg tccagaaact gagtgaaaat aatattcaga 300
caatttttgc agttactgaa gaatttcagc ctgtttacaa ggagctgaaa aacttgatcc 360
ctaagtcagc agtaggaaca ttatctgcma attctagcaa tgtaattcag ttgatcattg 420
atgcatacaa ttccctttcc tcagaagtca ttttggaaaa cggcaaattg tcagaaggmg 480
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gaaaatgttc caatatttcc attggagatg aggttcaatt tgaaattagc ataacttcaa 600
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aagtagaggt tattcttcag tacatctgtg aatgtgaatg ccaaagcgaa ggcatccctg 720
aaagtcccaa gtgtcatgaa ggaaatggga catttgagtg tggcgcgtgc aggtgcaatg 780
aagggcgtgt tggtagacat tgtgaatgca gcacagatga agttaacagt gaagacatgg 840
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tcttgactct gatgtatttt awcaggttgt gtgcatgaaa tttttataga taaagragtt 2940
gaggaaanaa aaaaanaaa 2959

<210> 271
<211> 2025
<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (1339)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1916)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1944)
<223> n equals a,t,g, or c

<400> 271
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tctgactttt aataatggta ataggaaaac aaaacccaaa gcttttcaga acttcagtgt 120
gaggtttcct attttracaa gttaacttgt aaatactcag gttttacgat gtataattta 180
cctaatagac caaactaact catggagata ttttgaacta ttatttaggt acaaacttta 240
taaagaatgt tagtatgtca taaaatataa cattacagct tatttaaaac caaatatagt 300
tgaacatatt taaaatacat tttcacagaa tggatgaatt agttgtttct tcagagttac 360
ttatgaacag ttgaatgctt taaaatgttc tgtctgtagg taacatctaa aacacaagtg 420
ggtttattta aatttttaaa atttgaaatt ttttatttgc aaaaaattgt tttatgcttt 480
attatatcgc aaatgagtgt cagatttttg agtaccaatg atcatgcttc catttttttt 540
agttttaaac caccaaacca atatttttcc tttaaatttt aatcttataa tatagaaatc 600
ttatgtaaat gaaattttgt catgtttcaa ataaagagaa ctgaagtaga aaatagaaat 660
gccagtaaac aacataatgt ttaatttaca acttacatta ggggtttggg ggaatgctaa 720
ttatatattg agaatataca ttagaactct tcaaaatggg ctcttctaat gaggtcacta 780
ctgaacaaaa ttgttccctc ttctgttaaa tagaataggt ttaaatgact agtcaaatga 840
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catggaaatg tatttaaagt ttttgcttgt gtcctcctca gtcagaatag aaaagtaact 1140
gaaatactct tacctttctg tccttgataa aatagtaaag aaaaccaaac aaacccaggc 1200
ctgatgggaa aaatgattcc tttattctag caacttactt tctgttggta tgggaaatgt 1260
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cttgtgtaac agaagatact ctttttttatg ctccttactg tgatcacaga aaaattaaaa 1620
atccaagtgc tctctagatt tgttgataaa cattttatgc ttgcatttaa acttgaaatg 1680
tatgagcaga atgagacaat cagttaaatc agaaatgaga agtattataa tgtaaaggcc 1740
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ttaaaagtgc tgstatgaaw atttttggct ataaaatttt accctgactt gstttcaata 1860
actgttacgt aatgcagttt gatgttgtaa cctaacattc caaaaaaaaa attganaggg 1920
ggaatctcaa aatagtatat actncactaa cttgtttaca ggtgctgtat ttaaaagcat 1980

gcttctctct caaaaagaaa aattaaagga ttttattgcc aaacc 2025

<210> 272
<211> 852
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (767)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (769)
<223> n equals a,t,g, or c

<400> 272
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gtgawgggac tatagacatg agccatcgtg cytggccttc ttgawtcttg aatacggggt 180
tttgaggtga aagcatttca tgaaaactta agttcataca caagagcatc atgaatattc 240
taaaagaggt atctgtgctt tttttgtgac cacaaaatat tacttcttat gaaatgttta 300
cactaggtga ggaaaagttc attaattacc tttaaaccgt tccttatttt ttttaagatt 360
ttaaattgta ttttggcttt tgcctccagt atcctttctg gttgctctgg tttgaattaa 420
gttcctatta tgctgcagca catatcaacc ttccctaagt aaccatttcc tggaatgtga 480
agcatcggtg ccattagcag accatatgca gaaatgtcgt gtacttgcat ttcttttttg 540
tgcactctat aaggctggtt gtgactcaga tcagcttaac tttttatatt atgttatttc 600
actaactgct acagtcaaaa tgatcaaatc tttgtacaat agaaaattat ttaaatttta 660
tttttctact gacatttcta attctagtgt aaatgtttat caataaaaaa ttactttcaa 720
ttctgagttg gaattatatt tctttttggt ggctaaatga ggttaancnt ttggaataaa 780
aaatgacttc aagttttcaa tttttaaaaa taacttaaaa atcttagcaa gggggaaact 840
tttttttaag gg 852

<210> 273
<211> 571
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (7)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (535)
<223> n equals a,t,g, or c

<400> 273
gcccaantac tttccagccc agtaaggggt atttcaggag agcagtccac tkaaggttct 60

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ggccgcatca aggtggtctt tactccgagc atctgtaaag tgacctgcac caagggcagc 180
tgtcagaaca gctgtgagaa ggggaacacc accactctca ttagtgagaa tggtcatgct 240
gccgacaccc tgacggccac gaacttccga gtggtaattt gccatcttcc atgtatgaat 300
ggtggccagt gcagttcaag ggacaaatgt cagtgccctc caaatttcac aggaaaactt 360
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ggcaaggcat tggggacgca tgtcatccat tcaacacata ccttgcctct gaccgtgact 480
agccagcagg agtcaaagtg aaatttcctc cttaacatag tcaatatcca tgtgnaacat 540
cctcctgaag cttccgtcca gatacatcag g 571

<210> 274
<211> 710
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (667)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (689)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (701)
<223> n equals a,t,g, or c

<400> 274
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ctccagccag tcccactaag ccaaagacca gaatctgaga acagggatgg ggaaattatt 120
cctttctgtg gatgattatg cagctgggcc atgatttcac acccgggggc catgggctaa 180
gatggagggg aaggaaggaa tgtaatgtgt gccctctacc tcttcaccag gcatcatcct 240
ctcactggcc ctggctggca ttcttggcat ctgtattgtg gtggtggtgt ccatttggct 300
tttcagaagg aagagtatca aaaaaggtga taacaaggga gtcatttaca agccagccac 360
caagatggag actgaggccc acgcttgagg tccccggagc tcccggggca catccaggaa 420
ggaccttgct ttgggaccct acacacttcg gctctctgga cacttgcgac acytcaaggt 480
gttctctgta gctcaatctg caaacatgcc aggcctcagg gatcctctgc tgggtgcctc 540
cttgccttgg ggaccatggc caacccagag ccatccgatt cgatggatgg ggatgcactc 600
ttcagaccaa gccagcagga attccaaagc tgcttgctgt aaatgtgtga gattgtgaat 660
gggctgnatt ctggattcaa aaccagccng ctggtgggcc ntaaggttgg 710

<210> 275
<211> 595
<212> DNA
<213> Homo sapiens

<400> 275
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acgcaggagc aagcctttca tttccttggt gggggagggg ggcggttgcc tggagagggc 120
cggggtcggg gaggttgggg ggtgtcagcc aaaacgtgga ggtgtccctc tgcacgcagc 180
cctcgcccgg cgtggcgctg acactgtatt cttatgttgt ttgaaaatgc tatttatatt 240
gtaaagaagc gggcgggtgc ccctgctgcc cttgtccctt gggggtcaca cccatcccct 300
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tctccccacg aaggtatctc tgtgtcttac tctgtgcaaa gacgcggcaa aacccagtgc 420
cctggttttt ccccacccga gatgaaggat acgctgtatt ttttgcctaa tgtccctgcc 480
tctaggttca taatgaatta aaggttcatg aacgctgcga aaaaaaaaaa aaaaaaaatt 540
tgccctatca gtgagtcgga ttaattgtcc gcgcggccgg acatttagta gtagt 595

<210> 276
<211> 1172
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (119)
<223> n equals a,t,g, or c

<400> 276
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ttctgaagct gcttcctctt ataaaatagc ttttgccgaa acatagtttt tttttagcag 180
atcccaaaat ataatgaagg ggatggtggg atatttgtgt ctgtgttctt ataatatatt 240
attattcttc cttggttcta gaaaaataga taaatatatt tttttcagga aatagtgtgg 300
tgtttccagt ttgatgttgc tgggtggttg agtgagtgaa ttttcatgtg gctgggtggg 360
tttttgcctt tttctcttgc cctgttcctg gtgccttctg atggggctgg aatagttgag 420
gtggatggtt ctaccctttc tgccttctgt ttgggaccca gctggtgttc tttggtttgc 480
tttcttcagg ctctagggct gtgctatcca atacagtaac cacatgcggc tgtttaaagt 540
taagccaatt aaaatcacat aagattaaaa attccttcct cagttgcact aaccacgttt 600
ctagaggcgt cactgtatgt agttcatggc tactgtactg acagcgagag catgtccatc 660
tgttggacag cactattcta gagaactaaa ctggcttaac gagtcacagc ctcagctgtg 720
ctgggacgac ccttgtctcc ctgggtagga gggggggaa tgggggaggg ctgatgaggc 780
cccagctggg gcctgttgtc tgggaccctc cctctcctga gaggggaggc ctggtggctt 840
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ctgtaggcac ctctcacact gttgtctgtt actgattttt tttgataaaa agataataaa 1080
acctggtact ttctaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1140
aaaaagggcg gccgctcgcg atctagaact ag 1172

<210> 277
<211> 780
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (161)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (773)
<223> n equals a,t,g, or c

<400> 277
cgcggacaag gccaggctag ccttgagctc cgtcgggcag ggcgccggga ttggtgtccg 60
gcagagcgtg agccagcggt gcgamgtcgg cgagcgggag tgaaagaaga aaagctagag 120
agcgaaggca aagccgagga gagagggccg cggtcggcga nggaatctga ctgcacggtt 180
gcgtgcgctc acttccggag gctccctcag scgggcggct ccgstagtgg ctaaaggcaa 240
agcattccgg ggcgcggcgc atgaagttga gcttcgtccc tgctagccgc cgctttctcc 300
ccaaaaatac atcctagcct taatgtttat gcctccattg ccccagttct tatctgtttt 360
gctcaatgtc tcatagctac aagaaggcaa tttctgacga agccctccgt sccttccaaa 420
tggattattt tggcgggctt ycacccggac agtatgccac ccgaatgact ggacaagtgc 480
acgggagcgg ctgtcatttg cggagtgcgc cttgcgatct aggcgcctca cagcgmaayt 540
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tacagacatt ggggccacaa agccggtgga acaacgggag acggcttcct gagtgtcagg 660
tcctccaaga tgagcttaaa mttcgggtgg tgggcaggyt cgtaggcggg aaaggsccgt 720
gtccagatgr atgcaktcca tgtatatatt gatgaaagac acgtatacca ttnggtcaag 780

<210> 278
<211> 2375
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (9)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (920)
<223> n equals a,t,g, or c

<400> 278
cggcagcgna ccaagatggc ggcgccctgt gagggacaag cgtttgccgt agggttgaaa 60
agaattgggg tgcagtagtt cgctccccag aagggacccc ccagaaaatc cggcagctga 120
tagatgaggg gattgccccg gaagagggag gcgtggacgc gaaggacacg tctgccacat 180
cccagtcagt taatggatca ccccaagcgg aacaaccttc attggaatct acaagcaaag 240
aagccttctt tagcagagtg gaaacatttt cttctttgaa atgggcaggt aagccctttg 300
agctgtctcc actcgtctgt gcaaaatatg gctgggtcac agtggaatgt gatatgctca 360
agtgctctag ctgtcaagct ttctctgtg ccagtttaca accagctttt gactttgaca 420
gatataagca acgatgtgct gagctgaaga aagccttgtg tactgcccat gagaagttct 480
gtttctggcc agacagccca tccccagacc gatttgggat gttgccccctg gatgagcctg 540
ctattcttgt tagtgaattc ctagatcgtt ttcaaagcct ttgtcacttg gacctccagc 600
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tcaaattagg ctcagacatc caagtccacg tcactgcctg tattctctct gtgtgtggct 780
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<210> 279
<211> 2461
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (14)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1164)
<223> n equals a,t,g, or c

<400> 279
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acagcctgga atgagtttgc ttattaccca gtcactttcg tagtgaatgt tcaaacccca 180
aagcaaatgt ttgcatctcc ttgtccataa aggagaaagc caggttatag gagaaagaga 240
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gttataaaca gaagggcctc ttaggatttt gagctctcct gacaatgaag gaaaagctct 360
cttgagtata caagttccac actcattacc tttcagtggt gacccatcac ccactacaat 420
ttgttgaagg aagggagtgt cagagatatg ctttaaagtt gtactttagg ctgaaattct 480

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t 2461

<210> 280
<211> 2520
<212> DNA
<213> Homo sapiens

<400> 280
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aaaagaagaa cgcctgtcca tcgccttttt ataagtcctt ctctccacac ctaaaagcag 180
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acagttcaac acttttgaaa aatgacatga attttcatta aaaacccttt tcctatgttt 2460
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<210> 281
<211> 1448
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1427)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1432)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1440)

<223> n equals a,t,g, or c

<400> 281
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ccaagttccg gccagttcga cctcgaggat ccagaggtgg agacggtact acctcccagc 120
tctgttttcc atccccttca ggtccttcct cgggaggcgg cgaaggcggt ccaccctgcg 180
cgtgatcctt yatgcccggc ccctgcccct ccctccgggt ggaacttccc cctcaccgcc 240
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taccctattc acgctctgtg cttgtgccaa gggggcaatg gcggcttcct gtgttctact 360
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tatctacggc aatgagcctg agattgggga ggccctgaag gaggacgtgg gaccaggcaa 540
ggcggtgcct cgggaggagc tgtttgtgac atccaagctg tggaacacca agcaccaccc 600
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<210> 282
<211> 827
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (725)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (800)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (814)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (815)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (817)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (819)
<223> n equals a,t,g, or c

<400> 282
gcggacgcgt gggcggacgc gtgggtccaa gggaccccaa agctccaggg cagtttgggc 60
gtcctgtagt tgtcccccat ggaaaggaga aggaggcaga aagaagatgg aaagaaggaa 120
acttcaatgt ctaccttagc gatttgatcc cagtggatag agccattgaa gacaccagac 180
ctgctggatg tgcagagcag ctagttcaca ataacctccc aaccaccagt gtcatcatgt 240
gctttgtgga tgaagtgtgg tccactctcc tgagatctgt tcacagtgtc atcaatcgct 300
ctcctccaca cctcatcaag gagattctgc tggtagatga cttcagcacc aaagactatc 360
taaaagataa tttggataaa tacatgtccc agtttccaaa agttcggatt cttcgcctca 420
aagagagaca tggcttaata agggccaggc tggcaggagc acagaatgca acaggtgatg 480
tgttgacatt tttagattct catgtggaat gtaacgttgg ttggttggaa cctcttctgg 540
aaagagttta tttaagtaga aagaaagtgg cctgtccagt aatcgaagtc atcaatgata 600
aggatatgag ttacatgaca gtggataact ttcaaagagg catctttgtg tggcccatga 660
actttggttg gagaacaatt cctccagatg tcattgcaaa aaacagaatt aaagaaactg 720
atacnataag gtgccctgtc atggctggtg ggattggttt ctattgccaa aagttacttt 780
ttttgaactt ggaacatacn aacccttggc cttnnangnt ttggggg 827

<210> 283
<211> 524
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (518)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (524)
<223> n equals a,t,g, or c

<400> 283
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gatcaggcca ttggcctcct cgtggccatc ttccacaagt actccggcag ggagggtgac 120
aagcacaccc tgagcaagaa ggagctgaag gagctgatcc agaaggagct caccatkggc 180
tcgaagctgc aggatgctga aattgcaagg ctgatggaag acttggaccg gaacaaggac 240
caggaggtga acttccagga gtatgtcacc ttcctggggg ccttggcttt gatctacaat 300
gaagccctca agggctgaaa ataaataggg aagatggaga caccctctgg gggtcctctc 360

tgagtcaaat ccagtggtgg gtaattgtac aataaatttt ttttggtcaa atttaaaaaa 420
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480
aaaaaacaaa aaaaaaaaaa aaaaaaaaaa aaaaaaanac aaan 524

<210> 284
<211> 613
<212> DNA
<213> Homo sapiens

<400> 284
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cgtagaagac gccctcacct atctggacca ggtgaagatc cgctttggca gcgaccctgc 180
cacctacaac ggcttcctgg agatcatgaa ggagttcaaa agccagagca tcgatactcc 240
tggagtcatc agacgtgtct cgcagctctt ccacgagcac cctgacctca ttgttggatt 300
caacgctttt cttcccctcg gatatagaat agacattccc aagaatggca agttaaacat 360
acagtcgcct ctgacaagcc aggagaattc gcacaaccac ggggacggtg cagaggactt 420
caagcagcag gtgccgtwta aagaggacaa accccaggtg cccctggagt ccgattccgt 480
ggaattcaac aacgccatca gctatgtgaa taagattaaa acccgcttct agaccaccca 540
gaaattacag gtcattcctg gagatctgca cacstwccar aargarcarc tgaacacgag 600
gggccggcca ttc 613

<210> 285
<211> 533
<212> DNA
<213> Homo sapiens

<400> 285
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acctgcgaca gcgggtagca caggcctttc gggagggaga gaatacccag gttgcagagc 180
ctgaggcctg tgatcagatg tacgagagct tagcgcgact ccattcaaac tactacaaac 240
acaagtaccc tcgccccaga gacaccagct tcagtggcct gtcgttggaa gagtacaagc 300
tgatcctgtc cacagacacc ttggaagagc ttaaggaaat agataaaggc atgtggaaga 360
aactgcagga gaagtttgcc cccaagggtc ctgaggagga tcataaggcc tgagctcagg 420
ccttacctcg tgcacatacc taggtgtgga gtcttgtaca ttgccatcgt caataaaact 480
gccccagttt ccccttgaaa aaaaaaaaaa aaaaraaaaa gaaaaaagtc gac 533

<210> 286
<211> 2071
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (303)
<223> n equals a,t,g, or c

<400> 286
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aaataaaaag aggacccaga aggagatgga gcatgccatg ctaatccggc acgacgagtc 120

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cmcccgagag ctagagtaca ggcagctgca cacgttacag aagctacgca tggatctgat 180
ccgtttacag caccagacgg aactggaaaa ccagctggag tacaataaga ggcgagaaag 240
agaactgcac agaaagcatg tcatggaact tcggcaacag ccaaaaaact taaaggccat 300
ggnaatgcaa attaaaaaac agtttcagga cacttgcaaa gtacagacca aacagtataa 360
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gacactgaaa gatgagcaga caagaaaact tgccattttg gcagagcagt atgaacagag 480
tataaatgaa atgatggcct ctcaagcgtt acggctagat gaggctcaag aagcagaatg 540
ccaggccttg aggctacagc tccagcagga aatggagctg ctcaacgcct accagagcaa 600
aatcaagatg caaacagagg cacaacatga acgtgagctc cagaagctag agcagagagt 660
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taaagattga aaatttgata cattttacag aaactaattg tgatgtacat atcagtggtg 1440
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aagaacctgc tggcaagagt ttaacttgtc ttcagcatat tctgattgta tcataatcat 1560
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aaaaaaaaaa ggctttactt cttttgcatg cactttaaaa acaaaacaaa acatttttca 1980
ggttccaagg aaragcatga taactgtcag agcttttaat tatatttgta aataaaagtg 2040
ttcatcacaa aaaaaaaaaa aaaaaaaaaa a                                2071
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<210> 287
<211> 1966
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (56)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (788)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (1753)
<223> n equals a,t,g, or c

<400> 287
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ggacggcagt ctcgcrcggc tactgcagca ctggggtgtc agttgttggt ccgacccaga 120
acgcttcagt tctgctctgc aaggatatat aataactgat tggtgtgccc gtttaataaa 180
agaatatgga aactgaacag ccagaagaaa ccttccctaa cactgaaacc aatggtgaat 240
ttggtaaacg ccctgcagaa gatatggaag aggaacaagc atttaaaaga tctagaaaca 300
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gaaaaggagg caagaatatt aaggctctcc gtacagacta caatgccagt gtttcagtcc 420
cagacagcag tggccccgag cgcatattga gtatcagtgc tgatattgaa acaattggag 480
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caaccagcca gctcccgctc gaatctgatg ctgtggaatg cttaaattac caacactata 600
aaggaagtga ctttgactgc gagttgaggc tgttgattca tcagagtcta gcaggaggaa 660
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gctgccaaaa ccacttgtta aaaattgtac agagcctgta ggaaaatata gaaggttcca 1860
ttgggatgtt ggcctagttc tgtgtgggaa gacttagtgg attttgtttg tttttagata 1920
actaaatcgg ccaacaaatc accgttctgg cctatgggac cgggcc 1966

<210> 288
<211> 869
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (869)
<223> n equals a,t,g, or c

<400> 288
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agctgggccc tgtggtagga ggctggtaca aggttttgga tcggttcatc cctggcacca 120

ccaaagtgga tgcactgaag aagatgttgt tggatcaggg gggctttgcc ccgtgttttc 180
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caaactacag cgggattatc ctgatgccct tatcaccaac tactatctat ggcctgctgt 300
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tatcaacttt acacccatat cccagcaaat gccactcatc cccactcttc atagacacat 720
ttgttactct aaccctgcct aggcttcttg tagctccagc tctttagaga ctcccggaac 780
cctttatatg gtgcctcagt aaatatgtta ttaaatatgt aatccggaaa aaaaaaaaaa 840
aaaaaaaaaa aaaaaaaaaa aaaaaaaan 869

<210> 289
<211> 1105
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (34)
<223> n equals a,t,g, or c

<400> 289
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acccatctca gcatggcttt gatattctct acttcctggc ctttaaaaat gacctataat 180
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gttttctcag attaacaaat atgatggatt ccatggctga ccttggtgct taaaccagga 360
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ttaaactgga tatatacttt gagccttact taattcacag ataagttgac ttaactcagt 480
atttttattt caattaatga aaacagtcct cttttcaacc ccaggttgct tacattttgc 540
tggtctcccc aagtgaccat tggtggagac caattaatga aggaatgaaa ttcactttat 600
tgggactgtg gtattcaaca gagccacact taaccacttt ttccaatgaa gaatctccag 660
aatgataatg cccaaatatg gatggccaar aagaatttgt atctacggtg tgctttatgt 720
gtttttgaca ctgctgtatt ctgtgtgatc aagtgatttg sagctggttc caatgtkact 780
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gttccagagg tacaaacctc caata 1105

<210> 290
<211> 1982
<212> DNA
<213> Homo sapiens

<400> 290

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gctgggatga gatcctcgaa gctgtgtttt aacaaactcc actggagagt cccatattcc 180
ctcaaatttg ggaatcacga ccctgaacca ggttgggcct gaagcagtca actgaattca 240
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atttgatatt ttagtatttt ggtgtaaaag ccaacaggca aactttgcca ggtactgtgt 480
agaaactcga aaatgtgagg ccagtttgta cagttcagag gaaatgcttt aacgtagaat 540
cagatagctg gaagagatct tcgagggaaa gtaagttccc taaagtcaca tctatgtctc 600
ctagctcagt gttctttgtc attgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgat 660
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cattgttaac ttcctaaaac agaatttgaa ctttatcaac ctcaacgtgt atataaacta 1860
gatagtcctc aatactttat caacctcaac atgtatataa actagatagt cctcaaatac 1920
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aa 1982

<210> 291
<211> 2329
<212> DNA
<213> Homo sapiens

<400> 291
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agaaaaagaa aactctggcg ttagaggata tagaaaaata taagtacaat tgttacaaat 180
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aattggcagc acaaagaaaa cgccctctcc tgacttgtat tgtggcagtc tgaacgcccc 300
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acaaaacagc aaacttcagg taactatttt ggattgcaaa caggataatt aaatgttcaa 420
acaatctgat aaaataacca tttggaaact gcttggcctt ctgttctttt atttgattga 480
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tcagacttaa ttattttccc ttttacaagg gaacagggca tcctgaattt tagagccttt 780
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<211> 2424
<212> DNA
<213> Homo sapiens

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<221> misc feature
<222> (666)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1757)
<223> n equals a,t,g, or c

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<211> 2160
<212> DNA
<213> Homo sapiens

<220>
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<222> (470)
<223> n equals a,t,g, or c

<400> 293
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<211> 1257
<212> DNA
<213> Homo sapiens

<400> 294
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gcgtcttctg agagtcaggg tctaggtgct grakygcgca cgraggccga tgtagaggag 180
gaggccctga ggaggaagct ggaggagctg accagcaacg tcagtgacca ggagacytcg 240
tccgaggagg aggagtccaa ggacgaaaag gcagagccca acagggacaa atcagttggg 300
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gccctatctt ctgagaagaa agttcagtaa ttccctgaaa agtcaaggta aagatgatga 720
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<210> 295
<211> 1117
<212> DNA
<213> Homo sapiens

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aagctcacca ctgctcagga ggtgctggcc cgggcccgca acctgatttc acccaggatg 180
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<210> 296
<211> 468
<212> DNA
<213> Homo sapiens

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ctgaccttac ctgagtttct gtatgtgtat ttgcaagaca gttaatacta atccatcatc 420
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<210> 297
<211> 464
<212> DNA
<213> Homo sapiens

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<221> misc feature
<222> (80)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (458)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (461)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (464)
<223> n equals a,t,g, or c

<400> 297
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cttataaaat aaattttggg caaacawmaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa agggggggncc nttn 464

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<211> 2630
<212> DNA
<213> Homo sapiens

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<210> 299
<211> 1422
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
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<222> (16)
<223> n equals a,t,g, or c

<220>
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<222> (1205)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1367)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1381)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1398)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1401)
<223> n equals a,t,g, or c

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ttaataaatc ttttgaaatt tgcagaatta gattgtattg tgtattttcg gttaaatgat 900
aattgaatgt aaatatttag atgcagcacc atattttata acccagcttt agcatttctt 960
catattttaa ggaaaccccc cacctccttc ttttaagggc gcttcttgct ctctgaaatg 1020
ccctgctaaa tgcttctctt aattatttga ataaggtagt ttggaataaa gaaagaaaag 1080
atcactctac atacagatag taaacttaat ttgtgatcct atatatgaga cagtataaaa 1140
atmcagataa gttttagaaa gactcaaaac aatatgtaaa tgactgatgt ttgcattatt 1200
aaggnaract tgggatgttg ggtcaagagg ggaaagtgtt agtcaatcca ctttggagca 1260
atatcatgaa ggtcaattat aattccatat acctttcttt gatgccacag tcagagatag 1320
atacagttgg gtggccatgg gtgtgcccat acagacaatt tttggtnaat tgtttcagac 1380
nttcaggtct gagactgnca ntgctggggg gcctcctggg tt 1422

<210> 300
<211> 553
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (484)
<223> n equals a,t,g, or c

<400> 300
gcccacgcgt ccgatggttt cttctattca ggcttcaatg gacaggcacc ttcgggatca 60
aagtacagag cagtcaccat ctgatcttcc tcaaaggara acagaagttg tgagttcttc 120
tgcaaagtct gggagtcttc agactggttt gcctgaatct tttcctttaa ctggtggtac 180
tgaaaatttg aatacagaaa caactgatgg ctgtgtagca gatgcactgg gagcagcctt 240
tgccacaagg tcaaaagcac aaaggggaaa ttccgtggag gagcttgaag agatggatag 300
tcaagatgct gagatgacta acacaactga gccaatggat cactcttgat ttaattagag 360
gctaataaag gcagaatgtt tattgtgaat atgtaatatt tgttggctgg gccacgtaac 420
ttgattagtc attaaaaatc ttgtacgtat ataaaaagat tatatcttgt tattcagtgc 480
atgntagcaa gtgtgtgatt ggccatagct tttaatatac tgctgcccag gctggctctg 540
aatttctata aat 553

<210> 301
<211> 464
<212> DNA
<213> Homo sapiens

<400> 301
ctcaaaaatc accagaaaac tcatactagt gaaaaatcct ataaatgtaa tgaatgtaga 60
aaggccttta gttactgctc tggtcttatt caatgtcagg tcattcatac tatagaaaaa 120
ccttatgaat acggtaaatg tggcaaagcc tttaggcaga ggacagacct taaaaaacat 180
cagaaaatgc ataccgarga gaaaccctat gaatgtaatg aatgtgggaa agcctttagc 240
cagagcacat atcttacaaa acaccaaaaa attcatagtg aagagaaatc aaatatacat 300
actgagtgtg gggaaaccwt twgrcaaaac tcttcttttt tacaacaata aaaacctcac 360
actggagaga ttctctgaat gccttaagaa tttggttaat atggagaccc ttcccagggg 420
aaccagaagg aggatcgtga aaacctgttg actacttaga tgat 464

<210> 302
<211> 2018
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1997)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2012)
<223> n equals a,t,g, or c

<400> 302
gccacatccc ggcagccctc ctacckgcgc acgtggtgcc gccgctgctg cctcccgctc 60
gccctgaacc cagtgcctgc agccatggct cccggccagc tcgccttatt tagtgtctct 120
gacaaaaccg gccttgtgga atttgcaaga aacctgaccg ctcttggttt gaatctggtc 180
gcttccggag ggactgcaaa agctctcagg gatgctggtc tggcagtcag agatgtctct 240
gagttgacgg gatttcctga aatgttgggg ggacgtgtga aaactttgca tcctgcagtc 300
catgctggaa tcctagctcg taatattcca gaagataatg ctgacatggc cagacttgat 360
ttcaatctta taagagttgt tgcctgcaat ctctatccct ttgtaaagac agtggcttct 420
ccaggtgtaa stgttgagga ggctgtggag caaattgaca ttggtggagt aaccttactg 480
agagctgcag ccaaaaacca cgctcgagtg acagtggtgt gtgaaccaga ggactatgtg 540
gtggtgtcca cggagatgca gagctccgag agtaaggaca cctccttgga gactagacgc 600
cagttagcct tgaaggcatt cactcatacg gcacaatatg atgaagcaat ttcagattat 660
ttcaggaaac agtacagcaa aggcgtatct cagatgccct tgagatatgg aatgaaccca 720
catcagaccc ctgcccagct gtacacactg cagcccaagc ttcccatcac agttctaaat 780
ggagcccctg gatttataaa cttgtgcgat gctttgaacg cctggcagct ggtgaaggaa 840
ctcaaggagg ctttaggtat tccagccgct gcctctttca aacatgtcag cccagcaggt 900
gctgctgttg gaattccact cagtgaagat gaggccaaag tctgcatggt ttatgatctc 960
tataaaaccc tcacacccat ctcagcggca tatgcaagag caagaggggc tgataggatg 1020
tcttcatttg gtgattttgt tgcattgtcc gatgtttgtg atgtaccaac tgcaaaaatt 1080
atttccagag aagtatctga tggtataatt gccccaggat atgaagaaga agccttgaca 1140
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ccagatgaaa atgaagttcg aactctcttt ggtcttcatt taagccagaa gagaaataat 1260
ggtgtcgtcg acaagtcatt atttagcaat gttgttacca aaaataaaga tttgccagag 1320
tctgccctcc gagacctcat cgtagccacc attgctgtca agtacactca gtctaactct 1380
gtgtgctacg ccaagaacgg gcaggttatc ggcattggag caggacagca gtctcgtata 1440
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gtgctttcga tgaagtttaa aacaggagtg aagagagcag aaatctccaa tgccatcgat 1560
caatatgtga ctggaaccat tggcgaggat gaagatttga taaagtggaa ggcactgttt 1620
gaggaagtcc ctgagttact cactgaggca gagaagaagg aatgggttga gaaactgact 1680
gaagtttcta tcagctctga tgccttcttc cctttccgag ataacgtaga cagagctaaa 1740
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aggcctgcga cgaactggga atcatcctcg ctcatacgaa cttcggctct tccaccactg 1860
attttaccac acactgtttt ttggcttgct tatgtgtagg tgaacagtca cgcctgaaac 1920
tttgaggata actttttaaa aaaataaaac agtatctctt aatcactgga aaaaaaaaaa 1980
aaaaaaaaaa aaaaccncgg gggggcccc gnacccca 2018

<210> 303
<211> 658
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (621)
<223> n equals a,t,g, or c

<400> 303
gacatttagg aacaattgca cttttaaagg gagagaatgc atagttgctc acatatctca 60
gtgtcagtca cctaacatgg atcagtgctt tatttgagat tacaaaacta gaaaatgacg 120
gagtcaaggc taggaccaat attctgttca gtcttagata attatagaat acacattaaa 180

atcagatatt tgaattttct taattttgta actatttgtc attgaaagga gatactaaaa 240
aaattatata tcgtcctaga aagtacatga actaataatg catttctaaa ggtgaaaaaa 300
gaataggtat ttttctgttt aatattcaat ttatagagag tagtacgtta atttttttaa 360
accccagaag ctcaggatct tatcatttta aaagaaatta tcaccagttc tgtgtgagta 420
aataaagtat tataacactt tgtttttca tccatgatac cttgtattta cttacctgag 480
cttttttttct agggaaagaa aaatgctcag gtaataacag agccttgaaa aattkggatt 540
ttcaaaacta cctatttatg tataggcctt tagatcatct gatgttgaat actctttaag 600
tgatctaaag gcctacatat naaaaggtat ttttattaaa ttctggatta aacatttc 658

<210> 304
<211> 671
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (524)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (593)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (657)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (659)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (671)
<223> n equals a,t,g, or c

<400> 304
tttacttaat cttgcctagt cacaaaataa gatgtgcacc catggtttgg agagttccta 60
tattagctga gcagtgagat acactatttc caaacggtgc acacctacag tagctttgga 120
aatgagccaa tcactgtttt acttaatggt tcttatcagc atgcaaatat tgcttgaaag 180
ttatttcctt attcactgtt ttgttagtcc attttgttag gaaacattaa ttcctaaaaa 240
tttgttcaga ataattaaaa gtgaacattt ggtgctgata ctcaaaaacc tacaaatgta 300
gccatttaaa aagtaacatg tttttctccc ctgctcattg cctgggagaa tggaatttta 360
tataactacc tttctttgca aaaataacgg tcgtgtcgag ttggtggtga ttttggcatt 420
ccatcttgca ctggtttcta gtataggctt agaaataatt ggcaggtaat aatctttcca 480
gtcaagttgc aagggatgct tatttctctt caaaaaaaga catnctgcgg gattgagtag 540
aaaatttagg tcagtttggg agcttatttg aatattttct actacattgg agntagcagt 600
ctttttctgg atcagatcag tgcatggtta tctacagggt gaatgcttct tggtggngna 660

agatctagct n 671

<210> 305
<211> 1680
<212> DNA
<213> Homo sapiens

<400> 305
ccaaagtgct ggaattccag gcatgagcca ctgcgcccag tctacacact aattcttgtt 60
agcccaacag ctgttctgtt ctatctaccc ctcatttcac gctcaaggag tcatacctag 120
aatagttaca cacaagaggg aaactggaag ccaaacactg tacagtattg tgtagaaagt 180
cacctcccta ctccttttat tttacatgag tgctgatgtg ttttggcaga tgagctttca 240
gctgaggcct gatggaaatt gagataacct gcaaagacat aacagtattt atgagttata 300
tcttagttct tgaaattgtg gaatgcatga ttgacaatat atttttaatt tttatttttt 360
caagtaatac cagtactgtt taactatagc cagaactggc taaaattttt atattttcag 420
agttgaagtt ggtgaagaca ttcatgattt aaacaccaga tcctgaaagg ggttaaatct 480
actttgaaat gaatctgcaa tcagtatttc aaagcttttc tggtaatttt agtgatctta 540
tttgattaga ctttttcaga agtactaaat aaggaatttt aacaggtttt tattaatgca 600
cagataaata gaagtacagt gaggtctata gccattttat taaaatagct taaaagtttg 660
taaaaaaatg aatctttgta attacttaat atgttagtta agaacccgtc aagcttatat 720
ttgctagact tacaaattat tttaaatgca tttatctttt ttgacactat tcagtggaat 780
gtgtaagcta gctaattctt gttttctgat ttaaagcact tttaaatctt atcctgcccc 840
ctaaaaacaa aaggttttga tcacaagggg aaatttaaga ttgttaaccc tgtttttcag 900
aagggctact gttaattgca cataaacatg aaatgtgttt tcccctgtgt actaacacat 960
tctaggcaaa attcaaactt atagtggtaa agaaacaggt tgttcacttg ctgaggtgca 1020
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ctaaaattgt ttttctacca tatcaaatta aacaattcat gcctttatag ggtcaggcct 1140
acaatgaata ggtatggtgg tttcacagaa ttttaaaata gagttaaagg gaagtgatgt 1200
acatttcggg ggcattaggg tagggagatg aatcaaaaaa taccccctagt aatgctttat 1260
attttaatac tgcaaaagct ttacaaatgg aaaccatgca attacctgcc ttagttcttt 1320
tgtcataaaa acaatcactt ggttggttgt attgtagcta ttacttatac agcaacattt 1380
cttcaattag cagtctagac attttataaa cagaaatctt ggaccaattg ataatatttc 1440
tgactgtatt aatattttag tgctataaaa tactatgtga atctcttaaa aatctgacat 1500
tttacagtct gtattagaca tactgttttt ataatgtttt acttctgcct taagatttag 1560
gtttttttaaa tgtatttttg ccctgaatta agtgttaatt tgatggaaac tctgctttta 1620
aaatcatcat ttactgggtt ctaataaatt aaaaattaaa cttgaaaaaa aaaaaaacga 1680

<210> 306
<211> 782
<212> DNA
<213> Homo sapiens

<400> 306
gaattcggca cgagtgaagc attagaatga ttccaacact gctcttctgc accatgagac 60
caacccaggg caagatccca tcccatcaca tcagcctacc tccctcctgg ctgctggcca 120
ggatgtcgcc agcattacct tccactgcct ttctccctgg gaagcagcac agctgagact 180
gggcaccagg ccacctctgt tgggacccac aggaaagagt gtggcagcaa ctgcctggct 240
gacctttcta tcttctctag gctcaggtac tgctcctcca tgcccatggc tgggccgtgg 300
ggagaagaag ctctcatacg ccttcccact ccctctggtt tataggactt cactccctag 360
ccaacaggag aggaggcctc ctggggtttc cccagggcag taggtcaaac gacctcatca 420
cagtcttcct tcctcttcaa gcgtttcatg ttgaacacag ctctctccrc tcccttgtga 480

tttctgaggg tcaccactgc cagcctcagg caacatagag agcctcctgt tctttctatg 540
cttggtctga ctgagcctaa agttgagaaa atgggtggcc aaggccagtg ccagtgtctt 600
ggggcccctt tggctctccc tcactctctg aggctccagc tggtcctggg acatgcagcc 660
aggactgtga gtctgggcas gtccaaggcc tgcaccttca agaagtggaa taaatgtggc 720
ctttgcttct gttaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780
aa 782

<210> 307
<211> 1791
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (487)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (515)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1769)
<223> n equals a,t,g, or c

<400> 307
ggggattgtt cctgaaacat tcacgctgtc caatctccca catttcagaa ttggtgggag 60
tgtgcatttg attgttaata accagctggg ttacaccact ccagctgaaa gaggaaggtc 120
ttctttatac tgcagtgata ttgggaagct tgtgggctgt gccatcatcc atgtcaatgg 180
agacagccca gaggaagtgg tccgtgccac acgactggct tttgaatacc aacgccagtt 240
ccgcaaggat gtgattattg atctgttgtg ctacaggcag tggggccaca atgagctgga 300
tgagccattc tacaccaacc ccatcatgta caaaatcatc agagctcgaa agagcattcc 360
agacacatat gcagagcacc tcattgctgg cggactcatg acgcaggagg aggtgtctga 420
aataaaatcc tcctactatg ccaagttgaa tgatcactta aataacatgg cccactacag 480
gcccccntgc cctgaacctg caggcccayt ggcangggcc tggytcagcc agaagsgcaa 540
wtcaccacct ggagtacagg tgtgcccctc gacctcctgc ggtttgttgg catgragtyt 600
ktagaggtgc caagrgagyt gcagwtgcac agtcamctgy tgragacaca tgttcagtcc 660
agaatggaga agatgatgga cggaatcaag ctagactggg ccaccgcgga actcttgcct 720
tgggttcttt acttgctcaa ggttttaatg ttcgtctaag tggccaagat gttggtcgtg 780
gaactttcag tcagaggcat gcaatggtgg tttgccagga gacggatgac acctacatcc 840
ccctgaacca tatggaccca aatcagaagg ggtttctaga ggtcagcaac agccccctgt 900
cagaagaggc cgtcctggga ttcgaatatg ggatgagcat tgagagccca aagttactgc 960
ccctgtggga ggcacagttt ggcgatttct tcaatggtgc ccagatcatc tttgacacat 1020
tcatctctgg aggagaggcc aagtggctcc tacaaagcgg cattgtcatc ctccttccac 1080
atggctacga tggggctggg ccagaccact catcctgtcg aatagagcgt ttcctgcaga 1140
tgtgtgacag tgcggaagag ggggtggacg gagacactgt gaacatgttt gtggttcacc 1200
caacaactcc tgcacagtat ttccacttgc ttaggagaca gatggtccgg aacttcagaa 1260
aaccactcat tgttgcttcc cctaagatgt tactcargct cccggcagcc gtgtcaactc 1320
ttcaagaaat ggcaccagga acaacattta acccggtcat tggtgattca tctgtggatc 1380

caaaaaaggt taagaccctc gtkttctgct ccggcaaaca tttctactcc ctggtgaaca 1440
aagagaatct ctgggggcca agaagcatga ctttgccatc atccgagtag aggaactctg 1500
ccccttcccg ttggattctt tacagcaaga gatgagcarr tacaaacatg ttaaagatca 1560
tatttggagt caggaggaac ctcagaacat gggtccgtgg tcgtttgttt ctccaaggtt 1620
tgaaaagcag ctggcctgca agctccgtct ggtggccggc ccccttttgcc agtacccgct 1680
gtaggaattg gcacagttca cttgcaccag catgaagata tcctcgccaa gaccttcgyt 1740
tgatgatgat tttgaaggaa catatttcnt ttaggaatgg cattaggccc t 1791

<210> 308
<211> 723
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (705)
<223> n equals a,t,g, or c

<400> 308
gggcaagacc tcatgcctaa aaaataaaga gaaagcagag taaaactgga ctctgagata 60
ygactaaagt tctgtgtgat acgtgtgcct tatttagctc aagacattcc tggagcacct 120
ataaaaactg acttgtaatc caggctatgt ctctttttag cttcgtaatc tttggcaagg 180
ccattggatt cttcagctgt acaattagga gactcgatca ggtgattgcc tttctcagct 240
gtcagttctc taatttcagg cttggtagct tgtaggaact gaaattgcaa ttaaaacctt 300
tataaactca aactaaatca tgaattacag aaaaagtcca ttcttccaaa acttgatgtt 360
accacactta caagtttaaa atatgaagtc gactgtttaa aggattctgc atatattcta 420
gtgtgcacat tcagaaacat ttttcttgga aaaagtaccc aacatttttt ataactgcac 480
atattaattt attgccagaa taaattgcat tgcatgctaa ataaagtcag ataattcaaa 540
tccatttgct tttatgtagt ttttcttcta aatgtcaaca ttttggaatt aaaatgttta 600
tggttttata tgagggtagg aaatcttaac tgctttgggg ggtattgttt ataggctttt 660
tgttatgggg ccggtagttt tttaataggg ggattgccca tttcnaccgt ttgggggccc 720
ggg 723

<210> 309
<211> 533
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (393)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (396)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (463)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (527)
<223> n equals a,t,g, or c

<400> 309
aattcggcac gagcgacgtg gtgctgggcg ttgggaccct actttatcta gttcgggaag 60
ttgggttgtg gggtcatacc tgtctgtctg ctcccagctt tcttgggttt cttccgacgg 120
cgtggggcct cgctaaggaa ttcccggccc ctcagggcca cggctttagc ggtgtctttt 180
gcgagttctt cgtaagtaca tcttaaagct gtcaagatgg ttctagcaga ccttggaaga 240
aaaataacat cagcattacg ctcgttgagc aatgccacca ttatcaatga agaggtatgt 300
aaaatattgt atgraatata tatgattgta ttattgtcac tagcattggg aagatggctt 360
attcataatc cccgtattta tatgtatttt gangtngact taatacttgt gggtaaaagc 420
ccaaaggggt taacagtagg aggggtttat tggggaatta ccnccaactc aaattacttc 480
aaccttcctt aagggatttc ccaaaaaaaa aaaaaaccgg ggggggnccc cga 533

<210> 310
<211> 763
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (317)
<223> n equals a,t,g, or c

<400> 310
gtttggaata aagaaagaaa agtttactat ctgtatgtag agtgatctta atttgtgatc 60
ctatatatga gacagtataa aaatacagat aagttttaga aagactcaaa acaatatgta 120
aatgactgat gtttgcatta ttaaggaaaa cttgggatgt tgggtcaaga ggggaaagtg 180
ttagtcaatc cactttggag caatatcatg aaggtcaatt ataattccat ataccttttct 240
ttgatgccac agtcrgagat asaatacart ttgggtggcc atggatgtgc cccaatacag 300
tacacatttt tkggttnaaa tttgttttca gatcatttca tggaatcttt gaagtatctt 360
tgactctaac tttgacttgg tggtggacct tccttggttt ttataacacc taagagatat 420
cctttagaat tacatgtatt ttagcataag gaaattgaaa aagtaaaaca tactggtttt 480
tttcaacaag accatatgta aattaaatag tgaaatgtgt atgagtttca gtagaactgt 540
accatcaaca atgtttccat aaatatgcag agttctttct tttgtattgt tatttacaat 600
attgttaaat tgaatgcatt tgcaatttct aggattctaa agaattgagt acagaaagta 660
gcaattttat tatttgatga taatatgaga attactgtgc caatactgtt ttgataaata 720
aatagatttt taaaaataaa tgtattgtac ttattagtgt agt 763

<210> 311
<211> 3131
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (4)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (5)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (10)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (26)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (3128)
<223> n equals a,t,g, or c

<400> 311
gggnncaaan gctggagctc caccgnggtg cgtccgctct agaactagtg gatcccccgg 60
gctgcaggat tcggcacgag gccacttcct ggggccgccg gcggggccgc tggctgcact 120
cagcgccgga gccgggagct agcggccgcc gccatgtccc accagaccgg catccaagca 180
agtgaagatg ttaaagagat ctttgccaga gccagaaatg gaaagtacag acttctgaaa 240
atatctattg aaaatgagca acttgtgatt ggatcatata gtcagccttc agattcctgg 300
gataaggatt atgattcctt tgttttaccc ctgttggagg acaaacaacc atgctatata 360
ttattcaggt tagattctca gaatgcccag ggatatgaat ggatattcat tgcatggtct 420
ccagatcatt ctcatgttcg tcaaaaaatg ttgtatgcag caacaagagc aactctgaag 480
aaggaatttg gaggtggcca cattaaagat gaagtatttg gaacagtaaa ggaagatgta 540
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<211> 940
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<213> Homo sapiens

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<222> (135)
<223> n equals a,t,g, or c

<220>
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<212> DNA
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<223> n equals a,t,g, or c

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atttattcaa tatggtgtat ctctgagttc aatttaaaac aatccaactc agtaatattt 420
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gtagtattgg ttctcatctg tagagaactg acattggagc aaattttaag tctccccttt 540
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